NCDEU

NEW CLINICAL DRUG EVALUATION UNIT

39th New Clinical Drug Evaluation Unit Meeting Annual Meeting

The New Clinical Drug Evaluation Unit (NCDEU) Meeting is a scientific conference sponsored by the National Institute of Mental Health (NIMH) which brings together academic psychiatrist, psychologist, research pharmacists and nurses, investigators with pharmaceutical industry, and representatives from NIMH and the Food and Drug Administration, who are interested in psychopharmacology and broader areas of interventions and services research.

Abstract Poster Presentations

(All poster presentations are copied verbatim and appear in category ranking. Some abstracts are missing due to damaged diskettes or inproper formatting. A copy of any missing abstacts can be obtained via fax. Contact dingram@nih.gov.

Poster	Poster Title	First Author	Primary Funding Sourc
1	Pharmacotherapy in Psychiatric Practice	Harold A. Pincus, M.D.	John D. and Catherine T. MacArthur Foundation
2	Ten Year Prevalence Trends for Psychotropic Medications from Two Health Service Systems	Julie M. Zito	NIMH Service Research Gra R01 MH-55259
3	Effect of Clinical Pharmacist on Patient Length of Stay in a State Psychiatric Hospital	Daniel J. Still, Pharm.D.	
4	Psychometric Evaluation of a Four Factor Quality of Life Instrument	David P. Walling, Ph.D.	
5	Safety of Sertraline in Long-Term Treatment in Panic Disorder: A Multicenter Study	Mark Rapaport, M.D.	Pfizer, Inc.
6	The Effectiveness and Safety of Combined Treatment with Paroxentine and Clonazepam Compared to Paroxtine Alone for Panic Disorder: Interim Analysis	John J. Worthington, M.D.	

7	A Multicenter, Double-Blind Comparison of Nefazodone and Placebo in the Treatment of Panic Disorder	G. Cassano, M.D.	Bristol-Myers Squibb
8	Double-Blind vs Single-Blind Placebo Lead-in Periods During Panic Disorder Efficacy Trials	David Michelson, M.D.	
9	The Efficacy of Open Label Nefazodone in Patients With Panic Disorder	Lazlo Papp, M.D.	Bristo-Myers and NIMH Research Grants: MH-01397 MH-00416
10	Long Term Treatment of Panic Disorder: A Controlled Maintenance/Discontinuation Study	M.R. Mavissakalian, M.D.	NIMH Research Grant: R01-MH-42730
11	Discriminant Validity of the SCL-90 Dimensions of Anxiety and Depression	C. Don Morgan, Ph.D.	
12	Pharmacotherapy and Quality of Life Improvement: A Review of Sertraline Treatment of Mood and Anxiety	Jean Endicott, Ph.D.	
13	Comparison of the Functional Status of Patients with Severe Obsessive-Compulsive Disorder vs. Schizophrenia Pre- and Post-Treatment	Alexander Bystritsky, M.D.	Solvay Pharmaceuticals
14	Sertraline Treatment of OCD: A Combined Analysis of Placebo Controlled Trials	John Greist, M.D.	
15	Safety of Sertraline in Long-Term OCD Treatment: A Multicenter Study	Wayne Goodman, M.D.	Pfizer, Inc.
16	Efficacy of Sertraline in Long-Term OCD Treatment: A Multicenter Study	Lorrin Koran, M.D.	Pfizer, Inc.
17	Treatment of Obsessive Complusive Disorder (OCD) with Clonazepam and Sertraline versus Placebo and Sertraline	*Barbara A. Crockett, M.D.	Roche Laboratories, Inc.
18	Retrospective Follow-up Study of Body Dysmorphic Disorder	Katharine Phillips, M.D.	Brown University School of Medicine
19	Placebo-Controlled Fluvoxamine Trials in Pathological Gambling	Eric Hollander, M.D.	
20	National Trends in the Prevalence of Attention-Deficit/Hyperactivity Disorder and the Prescribing of Methylphenidate Among School-Age Children: 1990-1995	Linda M. Robinson, M.S.P.H.	Pharmacoeconomics and Pharmaceoepidemiology Research Unit, College of Pharmacy, Washington State University
21	Association of Homozygosity for Dopamine Transporter with poor Methylphenidate Response	Bertrand Winsberg, M.D.	

22	Rate Dependent Effests of Methylphenidate on Objective Indices of Activity and Attention in Children with Attention-Deficit/Hyperactivity Disorder	Carryl P. Navalta, Ph.D.	NIMH Research Grant: R01-MH-48343
23	Methylphenidate Dose-Dependently Decreases Blood Flow in the Cerebellar Vermis of Children with ADHD	Carl M. Anderson, Ph.D.	NIMH Research Grants: MH 48343 and MH-53636
24	Comparison of Methylphenidate Versus Placebo on Activity Levels of ADHD Boys On and Off Task in a Laboratory Setting	Ann Polcari, R.N., Ph.D. (c)	Copley Pharmaceutical, Inc.
25	Pharmacotherapy of Attention Deficit Hyperactivity Disorder (ADHD) in Psychiatrically Referred Girls	Louise Glassner Cohen, Pharm.D.	
26	Chronic Stimulant Treatment Effects on Weight Acquistion Rates of ADHD Children	Laurence L. Greenhill, M.D.	
27	Health Care Service Systems Variations in Youth Psychotropic Treatments for ADHD and Depression	Susan dosReis, B.S., Ph.D.(c)	Dissertation Fellowship Awa 5-R03-MH58470
28	Acoustic Startle and Prepulse Inhibition in Attention Deficit Disorder	Lenard A. Adler, M.D.	Department of Veterans Affa and NYU, School of Medicin
29	A Controlled Trial of Bupropion SR for Attention Deficit Hyperactivity Disorder in Adults	Timothy Wilens, M.D.	Glaxo Wellcome, Inc.
30	Effectiveness and Tolerability of Adderall in Adults with Attention Deficit Hyperactivity Disorder	T. Spencer, M.D.	Shire Laboratories, Inc.
31	Screening for Burden of Illness of Depression and Other Chronic Conditions in African-American Primary Care Centers	DiAnne Bradford, Ph.D.	Unrestricted Grant from Mer & Co., and RCMII grant 1P20RR11104
32	Relative Regional Glucose Metabolism at Sleep Onset is Altered in Depressed Patients	Daniel Buysse, M.D.	NIMH Research Grants: MH 24652, MH-01414 and AG-15138

33	More Sites or More Time? Approaching Optimal Enrollment Strategies in Multisite Clinical Trials	Richard Landin, Ph.D.	
34	Double Blind Variable Placebo Lead-in Period: Results From Two Antidepressant Studies	Douglas Faries, Ph.D.	
35	Placebo Response in Depression Studies: Do Previously Reported Predictors Have Any Utility?	Charles Wilcox, Ph.D.	Pharmacology Research Insti
36	A Review of Placebo-Controlled Efficacy Trials for Antidepressants as Evaluated by the FDA	Kalyan Ghosh, Ph.D.	
37	Differences Between Drop-outs and Completers in the Continuation Phase of A Clinical Trial	Shamsah Sonawalla, M.D.	NIMH Research Grant: R01-MH048483
38	Naturalistic Follow-up of Chronically Depressed Patients Who Discontinued a Double-Blind Trial Compared with Patients Remaining in the Trial	Alan Gelenberg, M.D.	
39	The Utility of the Structured Clinical Interview for DSM-IV Axis Disorders (SCID) in the Identification of a Homogenous Population of Patients with Major depressive Episodes	Robert A. Massing,	
40	A Comparison between Interactive Voice Response System-Administered HAM-D and Clinician-Administered HAM-D in Patients with Major Depressive Episode	David J. DeBrota, M.D.	
41	HAM-D $\leq$ 10 as a Goal of Antidepressant Treatment Evaluation	Max Fink, M.D.	NIMH Research Grant: MH55495
42	Identifying Sources of Outcome Variability in Clinical Drug Trials	Mary B. Hooper, B.A.	
43	A Dynamic Model for Evaluating Treatment Effectiveness from Observational Studies	Andrew C. Leon, Ph.D.	

44	Work and Social Adjustment Scale: An Alternative Quality-of-Life-Instrument	James C. Mundt, Ph.D.	
45	Effect of Diagnosis, Chronicity and Severity on Timing of Antidepressant Response	Jonathan W. Stewart, M.D.	
46	What Constitutes an "Adequate" Duration of Antidepressant Treatment?	David J. Brunswick, Ph.D.	
47	Are There Sex Differences in Outcome With Antidepressants?	Frederic M. Quitkin, M.D.	
48	Gender Differences in Mood During Tryptophan Depletion	Francisco Moreno, M.D.	
49	Comparative Cost Effectiveness Modeling of Serotonin Reuptake Inhibitors	H. George Nurnburg, M.D.	No Outside Funding
50	Utilization and Cost Comparison of Inpatient Antidepressant Drugs	Deborah Ackerman, M.S., Ph.D.	Research Grant HS-09551 jointly funded by AHCPR an NIMH
51	SSRIs Effects on Vigilance and Cognition	Jereon Schmitt, M.Sc.	Pfizer, Inc.
52	Effects of Nortriptyline on Verbal Acquisition in Outpatients with Major Depression	Nunzio Pomara, M.D.	NIMH Research Grant: MH-44194
53	Timing, Severity and Clinical Significance of New Signs and Symptoms Associated with Interruption of Selective Serontonin Reuptake Inhibitor Treatment: A Double-Blind, Placebo Controlled Trial	Jeffrey Apter, M.D.	
54	Comparing Fluoxetine's Efficacy in Improving Mood, Physical, and Social Impairment Symptoms Associated with PMDD Across Three Randomized, Placebo-Controlled Clinical Trials	Eileen Brown, Ph.D.	
55	Substitution of SSRI with Bupropion SR Following SSRI-Induced Sexual Dysfunction	Anita Clayton, M.D.	Glaxo Wellcome, Inc.
56	Sexual Dysfunction Associated with the Treatment of Depression: A Placebo-Controlled Comparision of Bupropion Sustained Release and Sertraline Treatment	Charles C. Coleman, M.D.	Glaxo Wellcome, Inc.

57	Sildenafil for Antidepressant Induced Sexual Dysfunction in Women	Paula L. Hensley, M.D.	No outside funding, medicati samples provided by Pfizer, I
58	Buspirone and Amantadine Treatment of SSRI Associated Sexual Dysfunction: A Randomized, Placebo Controlled Trial	David Michelson, M.D.	
59	Ginkgo Biloba Relieves Sexual Dysfunction Due to Antidepressant Drugs	David Wheatley, M.D.	Lichtwer Pharma UK Ltd.
60	A Placebo-Controlled Study of Fluoxetine vs. Imipramine in the Acute Treatment of Atypical Depression	Patrick J. McGrath, M.D.	
61	Bupropion SR in Dysthmic Disorder	David Hellerstein, M.D.	Glaxo Wellcome, Inc.
62	Deaths with Selective Serotonin Reuptake Inhibitor Treatment	Benjamin Roy, M.D.	
63	Superior Acute ECT Response in Psychotic Versus Nonpsychotic Unipolar Depressed Patients	Charles Kellner, M.D.	NIMH Research Grant: MH-55495
64	A Clinical Monitoring Format for Mood Disorders	Constance Guille, B.A.	
65	Potential Risk for polycystic Ovarian Disease in Menarchal Females taking Valproic Acid	Barbara L. Gracious, M.D.	Scott & White Clinic, Scott, Sherwood, and Brindley Foundation
66	Divalproex vs. Lithium in the Treatment of Bipolaar Disorder: A Nauralistic 1.7 year Comparison	S. Nassir Ghaemi, M.D.	Abbott Laboratories
67	Valproate vs. Lithium Pharmacotherapy in Bipolar Disorder Patients in Clinical Practice: A Retrospective Study	Robert Litman, M.D.	
68	A Comparison of brian Lithium Levels on Lithobid Versus Immediate Release Lithium	Michael E. Henry, M.D.	Solvay Pharmaceuticals
69	Effectiveness of Traditional Antidepressants is Suboptimal in the Depressed Phase of Bipolar Disorder	Alan G. Mallinger, M.D.	NIMH Research Grants: MH29618, MH49115, MH30
70	Valproate Treatment of Bipolar Depression	Frederick Petty, Ph.D.	
71	Topiramate as Add-on Adjunctive Treatment for Patients with Bipolar I or Schizoaffective disorder-biopolar type	K.N. Roy Chengappa, M.D.	

72	Quetiapine in the Treatment of Neuroleptic Dependent Serious Mood Disorders	Martha Sajatovic, M.D.	Zeneca Pharmaceuticals
73	Long-Term Olanzapine Treatment: Efficacy and Safety in manic Patients With and Without Psychotic Features	M. Tohen, M.D., Dr.PH.	
74	Changes in Health-Related Quality of Life of Patients with Bipolar Disorder Treated with Olanzapine	M. Namjoshi, Ph.D.	
75	Olanzapine Versus Haloperidol in Schizoaffective Disorder, Bipolar Type: Repeated Measures Analyses of Efficacy and Cognitive Function	Fan Zhang, Ph.D.	
76	Clinical Studies Confirm Preclinical Selectivity of M100907 for the 5-HT2 Receptor	Steve J. Offord, Ph.D.	Hoechst Marion Roussel
77	Haloperidol vs. Risperidone: An FMRI Study of Frontal Activation in Schizophrenia	Robert Risinger, M.D.	Janssen Pharmaceutical Foundation
78	Who Should Do Assessments in Treatment Trials? A Comparison of Clinician Versus Independent Assessors in a Multicenter Schizophrenia Treatment Study	Delbert Robinson, M.D.	NIMH Research Grants U01 MH39992 and MH41960
79	Relationship Between Mood Disturbance in Schizophrenia and Quality-of-Life	Scott W. Andersen, M.S.	
80	Polypharmacy in Patients with Schizophrenia	David A. Solomon, M.D.	
81	Response of Chronic Nonresponding Schizophrenia Patients to Olanzapine: Clinical and Neurocognitive Effects	Robert C. Smith, M.D., Ph.D.	
82	Long Term Efficacy and Saftey of Olanzapine in Patients with Inadequate Initial Response to Haloperidol or Olanzapine	Craig H. Mallinckrodt, Ph.D.	
83	Quetapine and Risperidone in Outpatients with Psychotic Disorders: Results of the QUEST Trial	Jamie Mullen, M.D.	Zeneca Pharmaceutical
84	Switching from Risperidone to Ziprasidone: An Interim Analysis of a 6-week Study	George Simpson, M.D.	
85	Switching from Olanzapine to Ziprasidone: An Interim Analysis of a 6-week Study	David Daniel, M.D.	

86	A 28-week Comparison of Ziprasidone and Haloperidol in Outpatients with Stable Schizophrenia	Rory O'Connor, M.D.	
87	Differing Side Effect Burden with Newer Antipsychotics	Peter Weiden, M.D.	
88	Effect of Chronic Olanzapine Treatment on the Course of Presumptive Tardive Dyskinesia	Bruce Kinon	Eli Lilly and Company
89	The Comparative Anti-Muscarinic-Like Adverse Event Profiles of Olanzapine and Risperidone Treatment in Patients with Schizophrenia Spectrum Psychosis	John Kennedy, M.D.	Eli Lilly and Company
90	Average Dose and Weight: Olanzapine vs. Risperidone	James M. Russell, M.D.	Unrestricted Grant from Pfiz Inc.
91	The Impact of Weight Gain on Quality of Life Among Individuals with Schizophrenia	David Allison, Ph.D.	
92	A weight Management Program for treatment of Olanzapine Related Weight Gain	M. Patricia Ball, R.N., C.M.S.	Eli Lilly and Company
93	Psychotropic Use in a State Psychiatric Hospital: An Assessment of Falls	Mary Borovicka, Pharm.D., B.C.P.P.	
94	Cognitive Effects of Olanzapine in Schizophrenic Patients	Ileana Berman	
95	Clinical Experience with Olanzapine in Ethnic Subgroups	Pierre Tran, M.D.	
96	Differences in Platelet Paroxetine Binding to 5-HT Uptake Sites in Agitated and Non-agitated Alzheimer's Disease Patients	Jacob Mintzer, M.D.	
97	Factor Influencing Charge in ADAS-Cog Scores in Patients with Mild to Moderate Alzheimer's Disease: Perspectives from Multinational Placebo Controlled Trials	Kevin Bellow, B.S.	
98	Olanzapine Reduces Psychosis and Behavioral Distrubances Associated with Alzheimer's Disease	Jamie Street, M.D.	
99	Preliminary Evaluation of AIT-082 in Patients with Alzheimer's Disease	Steven D. Targum, M.D.	NeoTherapeutics
100	Centerally Acting Antiemetics Reduced Gastrointestinal Side Effects in Alzheimer's Patients Receiving The Cholinesterase Inhibitor Rivastigmine	Neal R. Cutler, M.D.	Novartis Pharmaceuticals Co
101	Side Effects and Time Course of response in a Placebo-controlled Trial of Fluoxetine in Geriatric	Deborah L. Ackerman, M.S., Ph.D.	NIMH Research Grant: MH-53935

	Depression		
102	The Effect of Bupropion SR on the Quality of Life of Elderly Depressed Patients with Medical Illnesses	Molly Fortner, B.S.	Glaxo Wellcome, Inc.
103	Acoustic Measures of Speech in Geriatric Depression Treated with Sertraline or Nortriptyline	Murray Alpert, Ph.D.	

104	Behavior Problems and the Risk of Institutionalization among Demented Elderly: Evidence from a Medicaid Home and Community-Based Services (HCBSs) Program	V.L. Phillips, D. Phil.	
105	A Randomized Double-blind Comparision of Nortriptyline Plus Perphenazine vs. Nortriptyline Plus Placebo in the Treatment of Psychotic Depression in Late Life	Benoit H. Mulsant, M.D.	NIMH Research Grants: MH30915, MH49786, MH52247, MH01153 and MH01613
106	Clinical Improvement and Tolerability is Matintained Log term in Elderly Patients with Psychotic Disorders Treated with Quetiapine	Paul Yeung, M.D.	Zeneca Pharmaceuticals
107	An Assessment of the Efficacy of Venlafaxine Extended Release in Elderly Patients with GAD	V.J. Mahe	
108	Venlafaxine XR is an Efficacious Short- and Long-tem Treatment for Generalized Anxiety Disorder	J.T. Haskins	Wyeth-Ayerst Research
109	Efficacy of Sertraline in Long-term Treatment in Panic Disorder: A Multicenter Study	Anita Clayton, M.D.	Pfizer, Inc.
110	Psychometric Properties of the Social Phobia Inventory (SPIN): A New Self-Rating Scale	Kathryn M. Connor, M.D.	NIMH Research Grant: 1R01 MH-49339 and SmithKline Beecham
111	A Placebo-Controlled Study of Sertraline in Generalized Social Phobia	Michael Van Ameringen, M.D.	
112	Long-Term Safety of Paroxetine in Social Anxiety Disorder	David Carpenter, R.Ph., M.S.	
113	An Open-Label Trial of Tramadol in Generalized Social Phobia	Nicholas A. DeMartinis, M.D.	
114	Derivation of the SPAN: A Brief Diagnostic Screening Test for PTSD	Samantha Meltzer-Brody, M.D.	NIMH Research Grants: 1R0 MH-44740 and R01-MH-474
115	Valproate Treatment of Post-Traumatic Stress Disorder	Frederick Petty, M.D., Ph.D.	
116	Open-Label Topiramate Treatment of post Traumatic Stress Disorder	Jeffrey Berlant, M.D., Ph.D.	
117	Fluvoxamine in PTSD: Improvement in Physiological Reactivity in Trauma Cues	Phebe M. Tucker, M.D.	Solvay Pharmaceuticals
118	Fluvoxamine Treatment in Veterans with Combat Related Post-Traumatic Stress Disorder	Rodrigo Escalona, M.D.	

119	Bupropion SR vs. Placebo in the Treatment of PTSD	Lori L. Davis, M.D.	Glaxo Wellcome
120	A Randomized, Controlled Trial of Risperidone of Psychotic Features in PTSD	Mark B. Hamner, M.D.	
121	Placebo-Controlled Comparison of Citalopram and Sertraline in the Treatment of Anxiety Symptoms in Depressed Patients	Stephens M. Stahl, M.D., Ph.D.	
122	Depression Treatment and Long-term Prophylaxis With Citalophram: A Double-Blind, Placebo-Controlled Study	Alan G. Wade, MRC Psych.	
123	Citalopram Treatment of Paroxetine Intolerant Patients	Michael E. Thase, M.D.	
124	Use of Pindolol in Potentialing the Antidepressant Effects of Buspirone: A Randomized Controlled Trial	Robert M. Berman, M.D.	NARSAD
125	Pretreatment Anxiety Does Not Predict Response to Bupropion SR or Sertraline	A. John Rush, M.D.	Glaxo Wellcome, Inc.
126	Profile of Antidepressant Activity of Lamotrigine in Bipolar Depression: Results from Double-Blind, Placebo-Controlled Study	Jeffrey Apter, M.D.	Glaxo Wellcome Research ar Development
127	The Responsiveness of the Hamilton Depression Rating Scale	Douglas Faries, Ph.D.	
128	An Open-Label Trial of St. John's Wort in Obsessive Compulsive Disorder	Leslie H. Taylor, M.D.	OC Foundation and Alterra (hypericum perforatum donat by Upsher-Smith Laboratorie Inc.
129	St. Johns' Wort Impact On CYP3A4 Activity	Carol A. Roby, Pharm.D.	
130	Determination of SJW Differential Metabolism at CYP2D6 and CYP3A4, Using Dextromethorphan Probe Methodology	Benjamin Ereshefsky	
131	Determination of the Differential Effects of St. John's Wort on the CYP1A2 and NAT2 Metabolic Pathways Using Caffeine Probe Methodology	Nevin Gewertz	
132	Mirtazapine Treatment of Obessive-Complusive Disorder	Lorrin Koran, M.D.	
133	Contribution of the Menstrual Cycle to Instability of Depressive Severity	Annie Harvey, Ph.D.	Psychiatric Research Institute

134	Perimenstural Affective Symptom Patterns in Women Treated for Depression	M. Linda Hoes-Gurevich, M.S.N.	
135	Association Between Estradiol Levels and HRSD During Gonadotropin-Releasing Hormones Agonist Therapy	Julia K. Warnock, M.D., Ph.D.	
136	Differential Affective Symptom Response During GnRH Therapy for Endometriosis	David W. Morris, M.A.	
137	Adrenal Steriods during Ovarian Suppression and Relation to Depressive Symptoms	C. Richard Parker, Jr., Ph.D.	
138	Pramipexole in the Treatment of Markedly Depressed Outpatients	Peter Londborg, M.D.	
139	Pramipexole Augmentation in the Treatment of Unipolar and Bipolar Disorder	Jonathan Sporn, M.D.	
140	Fluoxetine Versus Sertraline and Paroxetine in Major Depression: Long-term Changes in Weight	Maurizio Fava, M.D.	
141	Long-Term Treatment of Bulimia Nervosa Following Acute Response: A Comparison of Fluoxetine Versus Placebo	Steven Romano, M.D.	
142	Activation of Stress-Responsive Hormones Associated with Interuption of Selective Serotonin Reuptake Inhibitor Treatment	David Michelson, M.D.	
143	Venlafaxine in the Treatment of Dysthymia: An Open-Label Study	David J. Hellerstein, M.D.	
144	Bupropion SR vs Placebo in SAD: Controlled Trial	Danielle Webster, R.N., C.S., M.S.	Glaxco Wellcome, Inc.
145	Olanzapine Safety and Efficacy in Patients with Borderline Personality Disorder and Co-Morbid Dysthymia	K.L. Camlin, L.S.W.	Eli Lilly and Company and Douglas Bond, M.D. Researc Endowment--CWRU
146	Saftey and Pharmacokinetics of Duloxetine in a Placebo Controlled Dose Ranging Study	L.A. Granier, M.D.	
147	Management of Depression Refractory to SSRI Treatment: A Survey of Clinicians	David Mischoulon, M.D., Ph.D.	
148	Annual Health care Expenditures and Compliance with Antidepressant Treatment in an MCO	James M. Russell, M.D.	Unrestricted grant from Pfize Inc.
149	Combined Psychotherapy and Pharmacotherapy for Major Depression: A Review and Meta-Analysis	Ivan W. Miller, Ph.D.	NIMH Research Grant: MH-44778

150	Atypical Antipsychotics: Longitudinal Changes in Inpatient Use	Stephen Saklad, Pharm.D.	Unrestricted educational grar from Janssen Pharmaceutical
151	The Use of Atypical Antipsychotic Agents in new york State Office of Mental Health Facilities	Gary M. Levin, Pharm. D.	
152	A Ten-Month Cost Comparison Between Olanzapine and Risperidone in Patients with Schizophrenia	Roslyn Martinez, PharmD.	
153	A Comparative Analysis of Risperidone and Olanzapine Dosing Patterns in the Soth Carolina Medicaid Program	Christopher M. Kozma, Ph.D.	Janseen Pharmaceutica Resea Foundation
154	Dosing Trends and Associated Schizophrenia-Related Health Care Costs form a State Medicaid Perspective: Risperidone versus Olanzapine	Brian Nightengale, Ph.D.	Janseen Pharmaceutica Research Foundation
155	Risperidone vs. Olanzapine: Discharge rates and Economic Considerations	Deanna L. Kelly, Pharm.D.	Janseen Pharmaceutica Resea Foundation
156	The Link Between Drug Attitudes, Compliance Behaviors, and Resource Use among Individuals with Schizophrenia	A. George Awad, M.D.	
157	Olanzapine vs. Clozapine: An International Double-Blind Study in the Treatment of Resistant Schizophrenia	Jean-Noë l Beuzen, M.D.	
158	Clozapine Therapy in Veterans	Martha Sajatovic, M.D.	
159	ECT in Clozapine Resistant Schizophrenia	Georgios Petrides, M.D.	
160	Efficacy and Tolerability of Quetiapine Compared with haloperidol in Schizophrenic Patients Partially Responsive to Convential Antipsychotic Treatment	Jeffrey Goldstein, Ph.D.	Zeneca Pharmaceuticals
161	Strategies for Switching form Conventional Antipsychotic Drugs or Risperidone to Olanzapine	Bruce Kinon, M.D.	Eli Lilly and Company
162	Switching from Conventional Antipsychotics to Ziprasidone: An Interim Analysis of a 6-week Study	Peter Weiden, M.D.	
163	Anticholinergic Differences Among Patients Receiving Standard Clinical Doses of Olanzapine or Clozapine	K.N. Roy Chengappa, M.D.	Lilly Research Labs, The Stanley Center for Innovative Treatment of Bipolar @ U. o Pitts. aNd NIMH research grants: MH-55106, MH-015(and MH-52247.

164	Iron and Neurolepic-Induced Partinsonism in Schizophrenic Patients	Ileana Berman, M.D.	
165	Neuroleptic Dose Requirements and Treatment Response in Schizophrenic Patients Comorbid for Substance Abuse	Nehal Vadhan, M.A.	NARSAD Young Investigato Award
166	Algorithms for Treating Anxiety in Patients with Chemical Abuse and Dependence	David Osser, M.D.	
167	Utility and Medication Interaction of Combined Naltraxone Fluoxetine Treatment in Depressed Alcoholics: A Pilot Study	Ihsan M. Salloum	
168	Effect of Buprenorphine on CYP3A Activity in Rat Liver Microsomes	Rami B. Ibrahim, R. Ph.	
169	Reduced Cue-Elicited Cocaine Craving and Relapses Following Tratment with Olanzapine	David A. Smelson, Psy.D.	Lilly Research Laboratory
170	Interaction Study to Evaluate the Safety of Methylphenidate for Treating Cocaine Dependence	Bonita Singal, M.D.	
171	Is Methylphenidate like Cocaine? Subjective Effects in Cocaine Dependent Volunteers	Robert Baker, M.D.	NIDA Research Grant: R01 I 10325
172	Agonist Treatment of Stimulant Abuse/Dependence: Concept and Clinical Trials	John Grabowiski, Ph.D.	NIDA Research Grants: R01 DA-09262 and DA-6143
173	ADHD, Stimulant Medications, and Parents Perception of Sleep Difficulty: Is there a relationship?	Lisa Efron, Ph.D.	
174	Clinician, Parent, and Child Prediction of Medication or Placebo in Double-Blind Depression Study	Carroll W. Hughes, Ph.D.	NIMH Research Grants: MH 39188 and MH-41115
175	Who Knows Best--Mothers or Others? Comparing Biological Mothers vs. Child Self Report to Other Primary Caretakers vs. Child Self Report on a new Structured Diagnostic Interview in a Minority Sample	Amy B. Rowan, M.D.	
176	Psychiatric Illness in Mothers who Bring children for Mental Health Care	M. Katherine Shear, M.D.	NIMH Research Grant: MH-56848
177	Psychopathology in Parents of Children and Adolescents Whose Explosive Irritability Responds to Divalproex	Stephen J. Donovan, M.D.	

178	Prescribing Pattern for Antidepressant Pharmacotherapy, Diagnosis of Depression, and Receipt of Psychotherapy Among Children and Adolescents: 1990-1995	David A. Sclar, B.Pharm., Ph.D.	Pharmacoeconoics and Pharmacoepidemiology Research Unit, Washington S University
179	Significance of Expressed Emotion in Drug of Adolescent Depression	Phillippe Weintraub, M.D.	NIMH Research Grant: 1K08 MH-01572 and Upjohn and Solvay Pharmaceuticals
180	Lack of Pharmacokinetic Interaction Between Desipramine and Aderenergic Agonists in Children and Adolescents	Louise Glassner Cohen, Pharm.D.	
181	The Children's Anxiety Rating Scale (CARS): A Reliability Study	Michael J. Labellarte, M.D.	NIMH Research Grant: N01-MH-60016 and Solvay Pharmaceuticals, Inc.
182	Development of the Tourette Disorder Scale (TODS)	David Sheehan, M.D., M.B.A.	NINDS Research Grant: NS-32067 and Tourette Syndrom Association, Inc. and Layton BioScience, Inc.
183	Spectroscopic Imaging in Pediatric Obsessive Compulsive Disorder	Kate D. Fitzgerald, B.A.	Joe Young, Sr. Foundation, NIMH Research Grant MH-01372 and the National Obsessive Compulsive Foundation
184	Safety and Efficacy of Sertraline in Long-Term Pediatric OCD Treatment: A Multicenter Study	Karen Wagner, M.D.	Pfizer, Inc.
185	Body Dysmorphic Disorder in Children and Adolescents: Clinical Features and Treatment Response	Ralph S. Albertini, M.D.	Unrestricted Educational gra from Solvay Pharmaceuticals
186	Clozapine vs. Olanzapine Treatment of Childhood Onset Schizophrenia	Marianne Wudarsky, M.D.	
187	Characteristics of Placebo Baseline Responders in Aggressive Conduct Disorder	Richard P. Malone, M.D.	NIMH Research Grant: K07-MH-00979
188	Divalproex Controls Aggression Across a Spectrum of Psychiatric Diagnoses	Benjamin Roy, M.D.	Abbott Laboratories
189	Hypertriglyceridemia and Endocrine Complications Associated with Propranolol Use in Psychiatric Patients	Jodi A. Worrel, Pharm.D.	
190	The Effects of Antipsychotic Medications on Triglyceride and Cholesterol Levels: A Preliminary Report	Donna A. Wirshing, M.D.	

191	Evidence of a Biologic Measure of Placebo Response	Elizabeth McGarvey, Ed.D.	
192	Sertraline Treatment in Non-Cardiac Chest Pain: A Randomized Double-Blind Trial	Indu Varia, M.D.	Pfizer, Inc.
193	Risperidone and Suppression of Choreoathetosis in Huntington's Disease and Levodopa-Induced Dyskinesia in Parkinson's Disease	Mahmoud A. Parsa, M.D.	Janssen Pharmaceutica Inc.
194	A 12-Week Open Trial of Donepezil Hydrochloride in Multiple Sclerosis Patients with Associated Cognitive Impairment	Yvonne M. Greene, M.D.	Pfizer, Inc. and Eisai, Inc.

Poster No. 1

Pharmacotherapy in Psychiatric Practice

Harold A. Pincus, MD[1], Max Sederer, B.A.[2], Ana P. Suarez, MPH[2], Terri Tanielian, M.A.[2], Ivan D. Montoya, MD[2]

[1]American Psychiatric Association, Office of Research, 1400 K Street, NW, Washington, DC 20005.

[2]American Psychiatric Association, Washington, D.C.

The objective is to characterize current psychiatric practice in the United States with a particular focus on characteristics of psychiatrists reporting different patterns of psychopharmacology and psychotherapeutic practices. This is of interest given that recent changes in mental health policy, advances in research, including the restructuring of the mental health care delivery and financing systems, and increased availability of psychotropic medications, are believed to have greatly impacted psychiatric practice. Differences in caseload profiles will be examined across psychiatrists with a high versus low proportion of patients being treated with medication. We hypothesize that those physicians with a high percentage of patients being treated with medications are more likely to be young, salaried and working in a public setting. Their patients are more likely to be in a managed care plan and funded from public sources. Further, we expect to find that these physicians are more likely to be treating patients with bipolar and psychotic disorders as well as patients in their first episode of schizophrenia or schizophreniform disorder.

Data on psychiatrists practicing in the U.S. were collected through the 1998 (N=1080; unpublished data) National Survey of Psychiatric Practice (NSPP). The 1998 NSPP survey was mailed to 1500 randomly selected members of the American Psychiatric Association (APA-professional association of psychiatrists.) Questions were asked on an aggregate level with questions on the number of hours the psychiatrists spend in various professional activities and the proportion of time spent in different work settings. Other items included the general characteristics of their patient caseload, the use of different types of treatments and the different financial arrangements characterizing their practices. Most items use the psychiatrist's last typical workweek as the frame of reference. Information regarding the psychiatrist's sociodemographic characteristics and training are available from the APA Membership File. Data from the 1998 will be weighted and analyzed using SUDAAN and SAS software.

Preliminary unweighted results from the 1998 NSPP indicate that 70% of respondents are male, have a mean age of 51, 18% are international medical graduates, and on average spend 27 hours per week in direct patient care. Additional analysis will characterize psychiatrists by their treatment modality at a caseload level based upon reported proportion of patients receiving medication and the proportion of patients being treated with different styles of psychotherapy. Further comparisons will examine differences in physician's demographics, practice setting, diagnostic profiles, and patient caseload profiles across treatment modality.

The practice of psychiatry continues to undergo substantive changes most likely as a result of various developments in the mental health care delivery and financing systems and treatment advances within the field.

Primary Funding Source: John D. and Catherine T. MacArthur Foundation

Poster No. 2

Ten Year Prevalence Trends for Psychotropic Medication from Two Health Service Systems

Julie M. Zito,[1] Safer, DJ,[2] dosReis, S[1] Gardner, J[1] Johnson, RE[3] Lynch, F[3] Boles, M[3]

[1]University of Maryland 100 N. Greene St. Baltimore, MD 21201;

[2]Johns Hopkins Medical Institutions, Baltimore, MD; [3]Kaiser Permanente Center for Health Research, Portland, OR

Objective: Stimulants, alpha-agonists (clonidine and guanfacine) and selective serotonin reuptake inhibitors (SSRIs) are commonly used psychotropic medication groups among youths with behavioral or emotional disorders. However, the extent of their use in various community settings has not been researched. This study measures the total annual prevalence across a ten year span in two service systems. Age- and gender-specific findings are featured.

Method: Medicaid administrative claims data from a large Mid-western state and medication dispensing records from a staff model HMO in the northwest region of the US are compared for youths < 20 years old. A ten-year period from 1987 through 1996 was selected. Prevalence was defined as the occurrence of one or more prescription claims or records during the study year per 100 youths eligible for services (continuous and non continuous enrollees).

Results: Within system trends: Between 1987 and 1996, both service systems showed a dramatic increase in the utilization of all 3 medication groups. For the HMO system, stimulants increased from 0.36% to 2.54% (7-fold); alpha agonists increased from 0.01% to 0.39% (39-fold); and SSRIs increased during the 9 years they were available from 0.004% to 0.97% (243-fold). For the Medicaid system, stimulants increased from 1.01% to 3.72% (3.7-fold); alpha agonists increased from 0.01% to 0.73% (73-fold); and SSRIs increased from 0.04% to 1.03% (26-fold). Youths aged 15-19 had relatively greater increased stimulant utilization than their younger counterparts. Gender trends from 1987-1996 show a narrowing of the male:female ratio from >6:1 to 4:1 for the HMO enrollees whereas the Medicaid population showed only a slight change.

Between system trends: Total psychotropic group prevalence is substantially greater for Medicaid than HMO enrollees for stimulants and alpha-agonists but is quite similar for SSRIs. The extent of a prevalence increase is more pronounced when the initial rate is low--a fact that is well illustrated by the stimulants. By 1996, alpha-agonist use is about one-quarter of the stimulant utilization despite dramatic increases during the 10 year period. Age and gender-specific prevalence show similar trends regardless of the health system.

Conclusions: These community-based data corroborate marketing and anecdotal reports of the marked increase in psychotropic utilization during the past decade in the US. Both regional and

health service system differences must be considered in explaining the variations in these prevalence data. Additional analyses currently underway will assess data from another Medicaid state population to clarify the relationship between regional differences and patient characteristics. Prospective models to collect information on the duration of treatment, complexity of the regimens and consumer satisfaction are crucial next steps in effectiveness research for emotional disorders of youth.

Primary Funding Source: R01 MH 55259 NIMH Services Branch

Poster No. 3

Effect of Clinical Pharmacist on Patient Length of Stay in a State Psychiatric Hospital

Daniel J. Still, Pharm.D[1], Dennis J. Pabis, Pharm.D.[1], and Stephen R. Saklad, Pharm.D.[1]

1. San Antonio State Hospital, Department of Clinical Pharmacology, Box 23991, 6711 S. New Braunfels Ave., San Antonio, Texas 78223

Abstract:

In an era of ever tightening health care budgets, the value of each departmental service must be carefully evaluated for benefit vs. investment.

This project tracked all therapeutic recommendations offered by clinical pharmacists to treating physicians for one year on 2 acute care patient units at San Antonio State Hospital. Using PalmPilot® technology, the following data was collected prospectively: Type of recommendation, prescriber, drug, intervention date, expected outcome of recommendation, source of intervention, documentation method, audit date, acceptance rate, and clinical patient impact. After the initial recommendation, the treatment team rated the change in the patient's clinical presentation on the pre-determined audit date according to a Clinical Global Improvement (Improvement) scale. From the database created during this ongoing project, the following information is reported: Total Interventions per clinical pharmacist (2.4 FTE), Expectation of recommendation vs. Clinical Impact, Type of Recommendation vs. Clinical Impact, Physician acceptance vs. Clinical Impact, and comparitive lengths of patient hospitalization between acute care treatment teams by presence or absence of clinical pharmacist input. Financial impact of the clinical pharmacist was calculated based on the pharmacist's effect on length of stay.

1,872 recommendations were recorded from two staff clinical pharmacists (12 months each) and 2 clinical pharmacy residents (2.5 months each), affecting 347 patients, averaging 5.4 recommendations per patient (range 1-31). Treatment teams staffed with a clinical pharmacist had an average patient length of stay 5.4 days shorter than those teams without a clinical pharmacist. Based on the average bed day cost of this hospital, the cost avoidance per clinical pharmacist FTE was $4.62 for each dollar spent on clinical pharmacy services.

These data suggest that clinical pharmacy services have a positive effect on clinical outcomes and reduce inpatient healthcare expenditures in this setting.

Poster No. 4

Psychometric Evaluation of a Four-Factor Quality of Life Instrument

David P. Walling, Ph.D.[1] Charles K. Klein, Ph.D.[1] Sheryl L. Bishop, Ph.D.[2] and Gerald McCleery, Ph.D.[1]

[1] Psychiatric Management Resources 501 Washington Blvd. 5th Floor San Diego, CA 92103

[2] University of Texas Medical Branch 301 University Blvd. Galveston, TX 77550

Assessment of quality of life is an increasingly important component in the evaluation of the efficacy of psychotropic medications. However, few of the instruments used to measure life quality have undergone rigorous psychometric evaluation to validate their use. The Quality of Life Enjoyment and Satisfaction Questionnaire is one measure that was originally designed for use in the assessment of depression (Endicott J, Nee J, Harrison W, Blumenthal R., 1993) and has recently been validated in individuals with serious mental illness (Bishop, S., Walling, D., Dott, S., Folkes, C., & Bucy, J., In press). The current study is further validation of its use in an SMI population. The present study encompasses n=801 subjects and provides an adequate sample size for more rigorous construct validation through factor and reliability analyses. Employment of both exploratory (i.e., the maximum number of possible dimensions allowed is unspecified) and restricted (i.e., the maximum number of possible dimensions allowed is specified) factor analyses was chosen to examine the inherent**,** as well as proposed**,** factor structure. Exploratory Principal Components factor analyses (PCA) of the 44 items (n=720 for all factor analyses) comprising the four core domains of Physical Activities, Subjective Feelings, Leisure Activities and Social Relationships indicated six factors accounting for 57.2% of *total* variance. Of these six, the first factor accounted for 36.4% of the total variance with the next factors accounting for 6.9%, 4.2%, 3.9%, 3.1% and 2.6% respectively. Of these six, four represented 'split factors', i.e., multiple homogeneous subsets of items within a core dimension. Exploratory Principal Factor analyses (PFA) indicated six factors in the final correlation matrix accounting for 100% of the *common* variance. Of these six, the first factor accounted for 69.8% of common variance with the next factors accounting for 11.5%, 6.5%, 5.5%, 3.8% and 2.9% respectively. Once again, four factors represented 'split factors.' Overall, the results provide positive additional support for the Quality of Life Enjoyment core subscales as valid and discriminating measures of the four proposed domains for severe mentally ill patients. Ultimately, assessment of quality of life will provide clinicians basic tools with which to enact and monitor the effectiveness of treatment in areas which are not traditionally well measured by clinical methods.

Poster No. 5

Safety of Sertraline in Long-Term Treatment in Panic Disorder: A Multicenter Study.

Mark Rapaport, M.D.[1], Robert B. Pohl, M.D.[2,] Robert Wolkow, M.D.[3], Arkady Rubin, Ph.D.[3,] Elizabeth Hackett, Ph.D.[3]

1. Department of Psychiatry University of California, San Diego, 8950 Villa LaJolla Drive, LaJolla,
   CA 92037
2. University Psychiatric Center Wayne State University, Detroit, MI
3. Pfizer Inc., New York NY

Objective: Panic Disorder often requires long-term treatment. Sertraline has been proven effective in several acute studies of Panic Disorder, with or without agoraphobia. The current study was undertaken to evaluate long-term efficacy and safety of sertraline treatment in Panic Disorder.

Methods: Outpatients with DSM III-R Panic Disorder who had completed one of 3 double-blind, placebo controlled 10-week studies were treated for 52 weeks with open-label sertraline. Responders were randomized to 28 weeks of double-blind, placebo-controlled treatment. Safety was evaluated by adverse events, laboratory test results, vital signs and ECG.

Preliminary Results: 398 subjects from 31 US centers entered the study; at week 52, 183 subjects were randomized, 93 to sertraline and 90 to placebo. In this 80-week study, the most common adverse events were headache, insomnia, malaise, upper respiratory track infection, and diarrhea. Most of the adverse events were mild to moderate in severity. The adverse events tended to occur early in treatment with occurrence of both new and previously reported adverse events markedly decreased with increasing duration of treatment. Long-term sertraline treatment did not result in any clinically significant changes in laboratory parameters, vital signs and ECG. Eleven percent of subjects discontinued the study due to adverse events or laboratory abnormalities in the open-label phase: 3% of sertraline subjects vs. 10% of placebo subjects discontinued for these reasons in the double-blind phase.

Conclusion: In this study, the long-term safety and tolerability of sertraline was demonstrated during 80-week treatment in outpatients with Panic Disorder. The efficacy of long-term sertraline treatment will also be reported.

Study Funded By Pfizer Inc.

Poster No. 6

The Effectiveness and Safety of Combined Treatment with Paroxetine and Clonazepam Compared to Paroxetine Alone for Panic Disorder: Interim Analysis

John J. Worthington, M.D., Naomi M. Simon, M.D., Mark H. Pollack, M.D.,
Patricia C. Marzol, B.A., and Michael W. Otto, Ph.D.
Massachusetts General Hospital, 15 Parkman Street, WAC 812, Boston, MA 02114

Background: In the past few years, the serotonin selective reuptake inhibitors (SSRIs) have become first line treatments of panic disorder. In clinical practice, as many as 50% of patients receiving SSRIs and other antidepressants for panic disorder are concomitantly prescribed benzodiazepines, typically high potency benzodiazepines such as alprazolam or clonazepam. Despite the widespread application of combined antidepressant and benzodiazepine therapy for panic disorder, there has been little systematic assessment of the safety and effectiveness of this strategy in general. Thus, this ongoing study will provide critical information through the first systematic evaluation of the combined pharmacologic treatment strategy for panic disorder, employing a prototypic SSRI, paroxetine, and the high potency benzodiazepine, clonazepam.

Method: The present study is a double-blind, randomized, placebo-controlled, three-arm 12 week trial of 69 patients comparing the efficacy of paroxetine (up to 40 mg/d) combined with clonazepam (up to 2 mg/d), to paroxetine plus placebo in the treatment of patients with panic disorder ± agoraphobia. The clonazepam is administered either a) acutely over 5 weeks and then tapered, or b) maintained during the 12 week course of treatment. In addition, the study examines the safety and tolerability of these treatment strategies including examination of the effects on outcome and emergence of withdrawal symptomatology in patients tapering clonazepam during concomitant antidepressant therapy.

Results: We will present an update on the initial 50 patients randomized to treatment. Primary outcome measures will include the Panic Disorder Severity Scale and CGI-Severity. In addition we will examine adverse effects and tolerability during initiation of treatment and during the benzodiazepine taper period (weeks 5-9). Preliminary analyses of the first 21 patients (71% female, mean age = 35, duration of panic disorder = 10 years) showed that at endpoint with the last observation carried forward method, responder status (CGI-S = 1 or 2 and 0 panic attacks) at week 12 was achieved by 14% of patients on paroxetine plus placebo, 50% on paroxetine plus continued clonazepam, and 65% on paroxetine plus acute phase clonazepam with taper. Drop-out rates in the first three weeks were higher in the paroxetine plus placebo group (43%) compared to the two benzodiazepine groups (7%), suggesting improved tolerability of the combined treatment strategy, although the total number of side effects reported by patients in the first three weeks were similar.

Conclusions: Preliminary analysis of this ongoing trial of combined paroxetine and clonazepam treatment strategies for the treatment of panic disorder suggested improved rates of remission in both the combined treatment groups compared with paroxetine alone at 12 weeks.

Poster No. 7

A Multicenter, Double-Blind Comparison of Nefazodone and Placebo in the Treatment of Panic Disorder

G. Cassano, M.D.[1] , O. Benkert, M.D.[2], A. Wade, FRCA[3], U. Lepola, M.D., Ph.D.[4], L. Bellodi, M.D.[5], L. Skoglund, M.D.[6], S. Ahrenstedt M.D.[7], M. Zibellini, M.D.[8], A. Torbeyns, Ph.D.[9], R. Marcus, M.D.[10]

[1] Ospedale S. Chiara, Pisa, Italy; [2] Psychiatric Clinic U. Munich, Munich, Germany; [3] Com. Pharm, Services, Glasglow, Scotland; [4] Kuopion Psykiatripalvelu, Kuopo, Finland; [5] Ospedale S. Raffaele, Milan, Italy; [6] Psykitarisk Mottagning Vårdcentrum, Vetlanda, Sweden; [7] Lä karhuset Hö torgscity, Stockholm, Sweden;

[8] BMS, London, UK; [9] BMS, Waterloo, Belgium; [10] Bristol-Myers Squibb, 5 Research Parkway, Wallingford, CT 06492

Background: Nefazodone is a 5-HT_2 antagonist, a serotonin reuptake inhibitor and norepinephrine reuptake

inhibitor that is currently indicated for the treatment of depression. Nefazodone treatment is associated with early anxiolytic activity and unique beneficial effects on sleep quality while preserving sexual functioning . Long-term efficacy in depressed patients as well as efficacy in hospitalized depressed patients have been demonstrated with nefazodone.

Methods: A multicenter, 12 week, double-blind, flexible dose study of outpatients with a DSM-IV diagnosis of Panic Disorder, with or without Agoraphobia was conducted at 23 European centers to evaluate the safety and efficacy of nefazodone compared to placebo. Patients who had at least 2 panic attacks during the two weeks of placebo run-in were randomized to either nefazodone or placebo. Nefazodone was initiated at 50 m g BID followed by a flexible-dose titration within an allowable dose range 100-600 mg/day. Primary efficacy analyses were performed at week 10 (endpoint).

Results: A total of 274 patients were randomized to double-blind treatment with nefazodone (n=135) and placebo (n=139). The primary efficacy rating was the Panic Attack Response (based on the number of full panic attacks within 2 weeks). At endpoint (week 10) nefazodone patients exhibited significantly ($p<.05$) greater improvement than placebo patients on the Panic Attack Response analysis. Nefazodone was also superior to placebo at endpoint on the mean reduction in the number of panic attacks from baseline ($p<.01$), on the number of patients with 50% reduction in panic attacks from baseline ($p<.05$) and the percentage of patients with no panic attacks ($p<.05$). The mean nefazodone dose at endpoint was 453 mg/day. Nefazodone was well

tolerated with only 4% of nefazodone patients discontinuing for an adverse event compared to 7% of the placebo patients. Adverse events occurring in greater than 10% and twice the incidence of placebo-treated patients were dizziness and somnolence. There were no clinically meaningful changes in laboratory values nor any significant changes in vital signs or ECGs between treatment groups.

Conclusion: In this study nefazodone was shown to be a safe and effective treatment for patients with panic disorder

Funding for the study was provided by Bristol-Myers Squibb

Poster No. 8

DOUBLE-BLIND VS SINGLE-BLIND PLACEBO LEAD-IN PERIODS DURING PANIC DISORDER EFFICACY TRIALS

David Michelson M.D. (1), Peter Holland M.D (2), Rosalinda Tepner R.Ph.(1), Craig Pemberton B.S.(1)
(1) Lilly Research Laboratories, Lily Corporate Center, DC 2423, Indianapolis, IN 46285
(2) Boca Raton Medical Research, 7280 W. Palmetto Park Rd. #303, Boca Raton, FL 33433

Objective: Blinded lead-in periods are typically required in anxiety and depression efficacy trials for practical reasons, as well as in an attempt to assess illness severity and reduce placebo response. Several reports have suggested that single blind lead-in periods are of limited value in reducing placebo responses in anxiety and depression efficacy trials, but relatively few comparisons of trials of similar design and conditions but differing in the lead-in period design have been reported.

Methods: Among several recent fluoxetine panic disorder studies, two trials contained provisions for an initial 2-week placebo lead-in. In one, raters conducting the evaluations to assess eligibility for randomization were unblinded to protocol design, while in the second raters conducting assessments were blind to all aspects of the trial design. In both trials there was a requirement for maintenance of the same minimum panic attack frequency, but in the second patients also had to maintain a panic disorder severity scale score of 12 (corresponding to moderate severity). Outcome results for the first trial have been previously reported (Michelson, *Am J Psychiatry*, 1998), while the second trial is ongoing. However, preliminary data concerning the numbers of patients enrolled and randomized and reasons for non-randomization are available, and we present an initial report of these data here.

Results: In the trial with the single-blind lead-in, 356 patients were entered at the initial visit and 243 (68%) patients were randomized, while 113 (32%) were not randomized. Of the non-randomized patients, 16 (14%) failed to maintain symptom severity requirements, while 97 were excluded for other reasons (e.g. loss to follow-up, abnormal laboratory results, patient decision). In the trial with double-blind lead-in phase, of 198 patients enrolled, 112 (57%) were randomized, and 86 (43%) were not randomized. Of the 86 non-randomized patients, 40 (47%) were excluded for failing to maintain severity criteria, with the remainder excluded for other reasons.

Conclusion: Use of a double-blind placebo lead-in and increased stringency results in somewhat higher rates of patient exclusion at the point of randomization and may be more effective in identifying patients with placebo-responsive illness. It seems likely that this will facilitate discrimination of drug effects from non-specific effects, although definitive examination of this question must await analysis of final efficacy data. Importantly, however, higher exclusion rates at the time of randomization increase the overall number of patients who must be recruited, potentially delaying completion, increasing costs, and increasing the resources needed for a study, thus adding ‘noise’ in the form of extra sites and longer periods of enrollment time which could obscure signal detection.

Poster No. 9

THE EFFICACY OF OPEN LABEL NEFAZADONE IN PATIENTS WITH PANIC DISORDER

Laszlo Papp, M.D., Jeremy Coplan, M.D., Jose Martinez, M.S., Jack Gorman, M.D.

Columbia University, New York State Psychiatric Institute,1051 Riverside Drive, Unit #14, New York, NY 10032 and Hillside Hospital, Glen Oaks, New York

BACKGROUND: High drop out rate due to side-effects is one of the main problems in the pharmacological management of panic disorder. Nefazodone is a novel antidepressant which inhibits presynaptic 5-HT reuptake and blocks postsynaptic 5-HT2 receptors. One of the main advantages of nefazodone is a favorable side-effect profile compared to other antidepressant medications; most importantly, nefazodone is not associated with sexual dysfunction and weight gain. The present study was designed to determine the efficacy and safety of open label nefazodone treatment in patients with panic disorder in a fixed-flexible dose design. It was hypothesized that nefazodone will have similar efficacy but better acceptability compared to other anti-panic medications.

METHODS: Patients meeting DSM-IV criteria for panic disorder with or without agoraphobia were enrolled in a 12 week, open, fixed-flexible dose design treatment study. The design called for a starting dose of 50 mg BID followed by weekly increments of 100 mg up to 150mg BID per day. Non-responders (defined as 3 or higher score on the CGI-I) at week 6 were further raised to a maximum of 300 mg BID per day unless side-effects prevented the increase. Patients had to be on 100 mg per day for at least four weeks in order to be designated as evaluable.

Baseline and weekly rating instruments included the CGI, HAM-A, HAM-D, SAFETEE and self-rating on the Panic Attack Diary (PAD). Response was defined as a rating of 1 (very much improved) or 2 (much improved) on the CGI-I.

RESULTS: Of the 19 patients who began the study and took at least one dose of the medication, four dropped out during the first week, none due to side-effects. Fifteen (8 men; 7 women) of the 19 patients completed at least 5 weeks of treatment and were considered evaluable. Seven (47%) of the 15 patients were rated responders resulting in an intent to treat (ITT) response rate of 37% (7/19). Seven patients became panic free and an additional 3 patients, while continuing to report limited symptom attacks, stopped having full blown panic attacks. The mean HAM-A score dropped from 17.3 at baseline to 7.7 at the end of the trial. The mean score for HAM-D dropped from 10 to 5.3. The average dose of nefazodone was 100 mg at the end of week one, 283 mg at week four, and 338 mg at week twelve. The most frequently reported side-effects, sedation, dizziness, blurry vision, headache, muscle tension, were mild and subsided by week four. None of the patients presented with initial hypersensitivity reaction.

CONCLUSION While the response rate was somewhat lower than that found with some other anti-panic medications, given its favorable side-effect profile, nefazodone may be a good alternative for patients apprehensive about potential side-effects.

Supported by Bristol-Myers Squibb Pharmaceuticals and by NIMH grants MH-01397 (L. Papp) and MH-00416 (J. Gorman)

Poster No. 10

Long Term Treatment of Panic Disorder: A Controlled Maintenance/Discontinuation Study

M. R. Mavissakalian, M.D.[1], J. M. Perel, Ph.D.[2]

[1]Case Western Reserve University, 11100 Euclid Ave., Cleveland, OH 44106

[2] University of Pittsburgh, Pittsburgh, PA

Background: The question of relapse and the intimately related issue of the need for and effectiveness of maintenance treatment are primarily relevant to patients who show marked and stable response, i.e., achieve remission with acute treatment. The aim of the present research was to conduct a controlled maintenance/discontinuation study of imipramine in panic disorder. The methodological advantages of this study are : a) homogeneous sample of patients with moderate to severe panic disorder with agoraphobia (where the effects of treatment specifically due to pharmacotherapy are most marked and reliable); b) uniform acute phase treatment in terms of dosage and duration; c) inclusion of only those patients who achieve remission characterized by a virtually asymptomatic state with no functional disability due to symptoms; d) at risk period of observation of twelve month duration and e) use of empirically validated and clinically meaningful response/relapse criteria.

Method: The first 56 patients to meet remission criteria and to be randomly assigned to double blind continuation or discontinuation after six months of imipramine treatment (2.25 mg/kg) were followed with planned assessments every two months for 12 months. There were no behaviorally oriented interventions or instructions any time during the 18 months of the study.

Results: Survival analysis was done to compare the estimated probability of not relapsing, of not experiencing a worsening or of completing the experimental 12 months on study medication. A Mantel-Cox test showed a significant (p .01) difference between maintenance treatment (N=29) and discontinuation (N=27) conditions for each outcome category.

Discussion: Results will be discussed in the context of the available long term follow-up and outcome literature and in terms of their generalisability to other antidepressants.

Funded by NIMH, grant number RO1-MH 42730-10.

Poster No. 11

Discriminant Validity of the SCL-90 Dimensions of Anxiety and Depression

C. Don Morgan, Ph.D

Department of Psychiatry and Behavioral Sciences, Kansas University School of Medicine-Wichita, 1010 North Kansas, Wichita, KS 67214

Objectives: Although self-report measures of anxiety and depression are used frequently in drug trials, such measures have long been criticized for inadequate factor structure and unacceptably high correlations with each other. While much of this research has utilized samples of heterogeneous psychiatric patients, there is recent evidence that use of homogeneous samples greatly improves discriminant validity. The chief objective of this study was to investigate the discriminant validity of the SCL-90 dimensions of anxiety and depression utilizing homogeneous clinical samples.

Design and Methods: The sample consisted of 120 patients with a diagnosis of unipolar depression and 54 patients diagnosed with generalized anxiety disorder. The SCL-90 was administered during the initial screening process and was not used to diagnose. The SCL-90 gauges psychopathology in nine primary dimensions, two of which are anxiety and depression. Factor analysis and tests of significance were then done to contrast the scores of these two groups of patients on the anxiety and depression subscales of the SCL-90.

Results: The depressed group scored significantly higher on the SCL-90 depression subscale (P<.001) compared to the anxiety sample. Similarly, the anxiety patients scored higher on the SCL-90 anxiety subscale (P<.001) compared to the depression group. A principal-components analysis with varimax rotation was also performed on the anxiety and depression subscales. A two-factor solution was found which accounted for 41.7% of the total variance and resulted in all items loading .40 or greater on at least one of the factors.

Conclusion: It appears that the use of mixed samples such as college students or individuals with various psychiatric diagnoses results in poorly defined factors on self-report measures of anxiety and depression. This study illustrates the importance of determining the effect of sample variables on self-report measures of anxiety and depression. Doing so can facilitate the development of improved instruments to more efficiently distinguish between depression and anxiety.

Poster No. 12

Pharmacotherapy and Quality of Life Improvement: A Review of Sertraline Treatment of Mood and Anxiety Disorders

Jean Endicott, Ph.D.[1], Mark H. Rapaport, M.D.[2], Richard L. O'Sullivan, M.D.[3], Cathryn M. Clary, M.D.[3], Roger M. Lane, M.D.[3]

[1]NY State Psychiatric Institute, Dept. of Research Assessment & Training, 1051 Riverside Drive-Unit 123, New York, NY 10032
[2]University of California, La Jolla, CA
[3]Pfizer Inc., New York, NY

Background: Although symptom rating scales are a necessary and important component of psychopharmacological research truly favorable treatment outcome requires accurate assessment of broader domains of change and improvement. Other domains of functioning (e.g. sense of well-being & life satisfaction), broadly conceptualized as quality of life (QOL), are increasingly recognized as clinically important. Despite this, exceedingly few randomized controlled treatment trials recently surveyed reported on QOL. Furthermore, it is important, in view of high rates of placebo response in various treatment studies, to determine if there may be other means to differentiate active from placebo treatment responders. The current analysis was undertaken to assess QOL findings from a range of sertraline treatment studies in mood and anxiety disorders in which The Quality of Life Enjoyment & Satisfaction Questionnaire (Q-LES-Q, a validated and sensitive measure for assessment of QOL in psychiatric treatment studies) was used in an attempt to differentiate classic symptom responder groups in comparator trials.

Method: We reviewed findings on the Q-LES-Q from sertraline controlled treatment studies across a spectrum of mood and anxiety disorders, including major depression, elderly depression, premenstrual dysphoric disorder, and panic disorder.

Results: Analysis of Q-LES-Q findings demonstrated significant improvements in QOL, (in addition to standard symptom ratings) with sertraline treatment in several mood and anxiety disorders. Results of Q-LES-Q in responders measured via standard symptomatic measures to sertraline, placebo and comparator drugs will be presented. For example, responders to sertraline in an elderly depression trial (overall N = 102, 58.8 % response) had significantly greater ($p < 0.05$) changes in endpoint and completer Q-LES-Q scores compared to nortriptyline responders (N = 103; 49.5 % response).

Conclusion: Sertraline, in addition to improving core symptoms of mood and anxiety disorders, improved QOL across a wide range of patient types. Assessment of QOL with the Q-LES-Q also appears to offer an additional means to differentiate responders to comparator treatments and discriminate QOL differences between placebo and drug responders. These results are discussed regarding implications for pharmacological treatment studies, long-term compliance, and pharmacoeconomic outcomes.

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Poster No. 13

Comparison of the Functional Status of Patients with Severe Obsessive-Compulsive Disorder vs. Schizophrenia Pre- and Post-Treatment

Alexander Bystritsky, M.D.[1], Robert P. Liberman, M.D.[2], Sanjaya Saxena, M.D.[2], Sun Hwang, M.S.[2], Charles J. Wallace, Ph.D.[2], Karron Maidment, R.N.[2], Tanya Vapnik, Ph.D., R.N.[2]

[1] UCLA Neuropsychiatric Institute & Hospital

300 Medical Plaza, Suite 2200; Los Angeles, California 90095-6968

[2]UCLA Neuropsychiatric Institute & Hospital, Los Angeles, California

Objectives*:* Both obsessive-compulsive disorder (OCD) and schizophrenia can cause marked functional disability. We sought to determine the comparative levels of disability in OCD and schizophrenic patients and evaluate functional improvements with treatment in these two populations.

Methods: The Independent Living Skills Survey (ILSS) and Lehman's Quality of Life Scale (LQLS) were administered to 21 OCD patients in the UCLA OCD Partial Hospitalization Program and to 32 schizophrenic patients in the Partners in Autonomous Living Day-Treatment Program, before and after treatment. OCD patients received intensive cognitive-behavioral therapy and pharmacotherapy, during a six-week period, while schizophrenic patients received pharmacotherapy and social skills training during a six-month period.

Results: Pre-treatment, OCD patients and schizophrenics had similar scores on every domain of the ILSS except health-related skills, which were lower in schizophrenics (p=0.03). Post-treatment, the two groups differed significantly on most ILSS domains, because of significantly greater functional improvements in OCD patients. OCD patients had significantly lower subjective LQLS ratings than schizophrenics, before (p=.0001) and after treatment (p=.05), but only OCD patients improved significantly after treatment (p=.007).

Conclusions: Patients with severe OCD and patients with schizophrenia are equally functionally impaired, but OCD patients experience greater significant functional improvement with multi-modal treatment in a shorter time frame than schizophrenia patients. Lower subjective quality of life ratings by OCD patients may result from their greater insight into their illnesses and higher expectancies for functioning than the schizophrenic patients.

This study was supported in part by a grant from Solvay Pharmaceuticals.

Poster No. 14

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Poster No. 15

Safety of Sertraline in Long-Term OCD Treatment: A Multicenter Study

Wayne Goodman, M.D [1], Peter Londborg, M.D.,[2], R. Bruce Lydiard, Ph.D., M.D.[3,]
Elizabeth Hackett, Ph.D.[4,] Robert Woldow, M.D..[4] Arkady Rubin, Ph.D.[4,]

1. Department of Psychiatry, University of Florida College of Medicine, U.S. Brain Institute, Suite L-4-100, 100 Newell Drive, Gainsville, FL 32611
2. Seattle Clinical Research, Seattle, WA
3. Medical University of South Carolina, Charleston, SC
4. Pfizer Inc New York, NY

Objective: Obsessive-compulsive Disorder (OCD) typically requires long-term treatment. The current study was undertaken to evaluate long-term efficacy and safety of sertraline treatment in OCD.

Methods: Outpatients with DSM III-R OCD were treated for 52 weeks with single-blind sertraline. Responders were randomized to 28 weeks of double-blind, placebo-controlled treatment. Safety was evaluated by adverse events, laboratory test results, vital signs and ECG.

Preliminary Results: 649 subjects from 21 US centers entered the study; at week 52, 224 subjects were randomized, 110 to sertraline and 114 to placebo. In this 80-week study, the most common adverse events were headache, insomnia, nausea, somnolence, and diarrhea. Most of the adverse events were mild to moderate in severity. Adverse events tended to occur early in treatment with occurrence of both new and previously reported adverse events markedly decreased with increasing duration of treatment. Long-term sertraline treatment did not result in any clinically significant changes in laboratory parameters, vital signs and ECG. Twenty-one percent of subjects discontinued the study due to adverse events or laboratory abnormalities in the single-blind phase; 5% of sertraline subjects vs. 11%% of placebo subjects discontinued for these reasons in the double-blind phase.

Conclusion: This study demonstrated the long-term safety and tolerability of sertraline during 80-week treatment in outpatients with OCD. The efficacy of long-term sertraline treatment will also be reported.

Study Founded By Pfizer Inc

Poster No. 16

Efficacy of Sertraline in Long-Term OCD Treatment: A Multicenter Study

Lorrin Koran, M.D. [1], Delbert Robinson, M.D.[2], Elizabeth Hackett, Ph.D.[3], Arkady Rubin, Ph.D.[3], Robert Wolkow, M.D.[3]

1. Department of Psychiatry and Behavioral Science, 401 Quarry Road, Stanford University Medical Center, Stanford, CA 94305
2. Hillside Hospital Research Center, New York, NY
3. Pfizer Inc, New York, NY

Objective: Obsessive-Compulsive Disorder (OCD) typically requires long-term treatment. The current study was undertaken to evaluate long-term efficacy and safety of sertraline treatment in OCD.

Methods: Outpatients with DSM III-R OCD were treated for 52 weeks with single-blind sertraline followed by randomization of responders (Y-BOCS decreased by at least 25% and CGI-Improvement of 1,2 or 3) to 28 weeks of double-blind, placebo-controlled treatment. Efficacy was evaluated by the Y-BOCS, NIMH global scale, CGI-Severity, CGI-Improvement, and Q-LES-Q (quality of life) ratings.

Preliminary Results: 649 subjects from 21 US centers entered the study; at week 52, 224 subjects were randomized, 110 to sertraline and 114 to placebo. More than 90% of responders to the first 16 weeks of therapy maintained considerable improvement during weeks 17-52 of single-blind treatment. Rates of discontinuation due to relapse or insufficient clinical response (9% in sertraline group vs. 24% in placebo group) and rates of acute exacerbation of OCD (12% in sertraline group vs. 35% in placebo group) were each statistically significant ($p<0.001$). Sertraline was statistically more effective than placebo as measured by change from double-blind baseline to endpoint on all the efficacy and the Q-LES-Q scores.

Conclusion: Sertraline was effective in long-term treatment in OCD for up to 80 weeks. Sertraline treatment was substantially better than placebo in prevention of worsening of OCD symptoms. In addition to the efficacy, the safety profile of long-term sertraline treatment will also be reported.

Study Funded By Pfizer Inc.

Poster No. 17

Abstract Title: Treatment of Obsessive Compulsive Disorder (OCD) with Clonazepam and Sertraline versus Placebo and Sertraline

Barbara A. Crockett, M.D.[1], Jonathan R.T. Davidson, M.D.[1] and Erik Churchill, M.S.[1]

[1] Duke University Medical Center, Department of Psychiatry, Box 3812, Durham, NC 27710

Background: This double blind, randomized, parallel comparative study investigates whether the additional use of clonazepam accelerates and increases the overall response in patients with OCD who are treated with sertraline. With an SSRI alone the response rate in OCD is between 38-43% and there is much residual morbidity[1]. Moreover, the rate of response remains slow. Given both the marked anxiolytic effects of clonazepam, as well as its serotonergic effects, there is good reason to expect that it may augment the effects of an SSRI in obsessive-compulsive disorder.

Method: 35 patients were randomized with 19 in the sertraline and clonazepam and 16 in the sertraline and placebo groups. Male and female outpatients, age 18-65 years, met criteria for a primary diagnosis of Obsessive Compulsive Disorder according to DSM-IV, as determined by the Structured Clinical MINI Interview. The excluded diagnoses were: bipolar disorder, severe personality disorders, psychotic disorders, drug/alcohol abuse or dependency, and other Axis I anxiety disorders. Patients had a baseline score of 7 or above on the NIMH Global Obsessive Compulsive Scale and 20 or above on the Y-BOCS. They must have had a CGI severity of illness rating of 4 or above. Patients were placed in a non-drug washout period of one week. They were then treated in a double-blind trial with sertraline and clonazepam or sertraline and placebo for 12 weeks. Sertraline was administered at 50 mg/day for one week, to increase to 100 mg/day thereafter. The dose was reduced in the event of troublesome side effects. Clonazepam and placebo were initiated at 0.25 mg/day for 3 days, increasing to a titration schedule for final maximum dosing up to 4 mg/day by day 26. The dose was reduced in the event of side effects. During weeks 12-16, all patients underwent a slow dose taper of clonazepam or placebo, while remaining on sertraline 100 mg. Appropriate efficacy ratings and safety parameters were measured at specific intervals throughout the study.

Results: The determination of efficacy was based primarily on changes from baseline to the last observation taken through week 12. Interim analysis revealed no significant difference between groups at endpoint on the Y-BOCS or HAM-A, but a trend ($p<0.1$) was seen on the CGI-Severity scale favoring sertraline and clonazepam.

Significance: Further studies of this compound in this treatment combination are warranted.

Source of Funding: Roche Laboratories, Inc.

[1]Greist JH, Jefferson JW, Kobak KA, Katzelnick KA, Serlin RC. Efficacy and Tolerability of Serotonin Transport Inhibitors in Obsessive Compulsive Disorder: A Meta Analysis. Archives of General Psychiatry 1995: 52:53-60.

Poster No. 18

33 Cases of Body Dysmorphic Disorder in Children and Adolescents: Clinical Features and Treatment Response

Ralph S. Albertini, M.D. and Katharine A. Phillips, M.D.

Butler Hospital/Brown University School of Medicine, 345 Blackstone Blvd., Providence, RI 02906

BACKGROUND: Body dysmorphic disorder (BDD), a preoccupation with a nonexistent or slight defect in appearance, usually begins during adolescence. Reported cases indicate that, as in adults, BDD in children and adolescents may lead to impaired functioning, psychiatric hospitalization, and suicide attempts. Several case reports suggest that SRIs may be effective in decreasing BDD symptoms and improving functioning in children and adolescents. Nearly all of the literature on BDD in children and adolescents, however, consists of case reports. In this study, we systematically assessed BDD's clinical features and treatment response in this age group in the largest series to date.

METHODS: 33 consecutive children and adolescents with DSM-IV BDD were assessed for demographic characteristics, phenomenology, associated psychopathology, and treatment history and response. Subjects ages 12-17 were assessed with the SCID-P; those ages 6-11 were assessed with the K-SADS-PL. Other scales used included the Children's Global Assessment Scale (C-GAS), the adolescent version of the beliefs sealy Yale-Brown Obsessive Compulsive Scale Modified for BDD, the adolescent version of the Brown of Assessment Beliefs Scale and the BDD Data Form (a semi-structured instrument that obtains information on the clinical features of BDD). Treatment response was assessed with the CGI.

RESULTS: Of the 33 children and adolescents, 3 were male and 30 were female. They had a mean age of 14.9 ± 2.2 years (range=6-17 years). The mean age of onset of BDD was 11.8 ± 2.6 years (range=5-17 years). Bodily preoccupation focused on a wide variety of body parts, most often the skin (61%) and hair (55%). 50% of the subjects had appearance-related beliefs that were delusional, and 79% had ideas or delusions of reference due to BDD. All subjects had associated compulsive behaviors, most often camouflaging (e.g., with clothing) in 94%, comparing with others (87%), and mirror checking (85%). 94% of subjects reported impairment in social functioning and 85% in academic functioning due to BDD with 18% dropping out of school (3% temporarily and 15% permanently) because of BDD symptoms. 39% had been psychiatrically hospitalized, 67% had experienced suicidal ideation, and 21% had made a suicide attempt. The most common comorbid lifetime diagnoses were major depression (73%), OCD (39%), and social phobia (30%).

Ten (53%) of 19 subjects treated with an SRI had much or very much improvement in BDD symptoms, and 10 (45%) of SRI trials led to much or very much improvement in BDD symptoms (7 of 12 fluoxetine trials, 1 of 4 paroxetine trials, 1 of 4 sertraline trials, 1 of 1

clomipramine trials, and 0 of 1 fluvoxamine trials. Six (43%) of 14 SRI trials in delusional patients led to much or very much improvement. Mean time to response was 8.0 ± 3.9 weeks (range = 4-16 weeks). In contrast, 0 of 8 trials with other psychotropic medications, 0 of 1 trials of cognitive-behavioral therapy, 0 of 2 group therapies, and 1 of 20 psychotherapy treatments resulted in improvement. Twelve (36%) subjects received surgical dermatologic, or dental treatment, with a poor outcome in all cases.

CONCLUSIONS: BDD is present and diagnosable in children and adolescents, and can cause significant morbidity. These preliminary data suggest that SRIs may be an effective treatment in this age group, although controlled treatment trials are needed to confirm this finding.

This work was supported in part by an unrestricted educational grant from Solvay Pharmaceuticals.

Poster No. 19

Placebo-Controlled Fluvoxamine Trials in Pathological Gambling

Eric Hollander, M.D., Concetta M. DeCaria, Ph.D., Jared N. Finkell, B.A.
Mount Sinai School of Medicine, One Gustave L.Levy Place, New York, N.Y. 10029

We have completed two studies to assess the efficacy and tolerability of the selective serotonin reuptake inhibitor (SSRI) fluvoxamine in the treatment of pathological gambling (PG). In the first, sixteen patients with PG were entered into an 8-week single-blind fluvoxamine trial. Of the ten patients that completed the trial, seven (70%) were judged treatment responders on fluvoxamine at the end of the study, in that they had greater than 25% decreases in their gambling behavior scores on the pathological gambling modification of the Yale-Brown Obsessive Compulsive Scale (PG-YBOCS) and their clinician-rated Clinical Global Impression scores for gambling severity (PG-CGI) were very much improved or much improved. Fluvoxamine treatment resulted in complete gambling abstinence in seven of the ten patients.

To further characterize and test the effectiveness of fluvoxamine in treating PG, a second study, a 16-week randomized placebo-controlled double-blind crossover trial of fluvoxamine, was conducted. Patients were randomly assigned to treatment with either fluvoxamine or placebo in Phase I and crossed over to the other drug condition in Phase II. In this trial, fluvoxamine was shown to be significantly more effective than placebo in reducing gambling urge and behavior as measured by the PG-YBOCS total score [$F=5.6$ ($df=1,8$) $p=.046$] and PG-CGI improvement score [$F=14.8$ ($df=1,8$) $p=.005$]. There was also a drug x phase order interaction as assessed by the PG-YBOCS total score [$F=13.2$ ($df=1,8$) $p=.007$] and PG CGI improvement score [$F=6.0$ ($df=1,8$) $p=.040$] such that both drug conditions were effective in Phase I, but in Phase II placebo lost its effectiveness whereas fluvoxamine retained its effectiveness. These two trials are the first controlled treatment studies in PG, and demonstrate that fluvoxamine is effective in acute trials in treating this debilitating and growing public health problem.

Poster No. 20

National Trends in the Prevalence of Attention-Deficit/Hyperactivity Disorder and the Prescribing of Methylphenidate Among School-Age Children: 1990 - 1995

Linda M. Robison, M.S.P.H.,[1] David A. Sclar, B.Pharm., Ph.D.,[1,2,3] Tracy L. Skaer, B.Pharm., Pharm.D,.[1,4] Richard S. Galin, M.D.[4,5]

[1]Pharmacoeconomics and Pharmacoepidemiology Research Unit, College of Pharmacy, Washington State University, P.O. Box 646510, Pullman, WA 99164-6510

[2]Program in Statistics, Washington State University, Pullman, WA

[3]Washington Institute for Mental Illness Research & Training, Eastern Branch, Spokane, WA

[4]Pullman Memorial Hospital, Pullman, WA

[5]Neuro-Psychiatric Institute, University of California at Los Angeles, Los Angeles, CA

Background: It has been reported that during the past decade the prevalence of attention-deficit/hyperactivity disorder (ADHD) (ICD-9-CM code 314.00 or 314.01) and its pharmacologic treatment have increased dramatically in the U.S. We used a single national data source to discern trends in the prevalence of U.S. office-based visits resulting in a diagnosis of ADHD, and trends in the prescribing of stimulant pharmacotherapy (including methylphenidate) for its treatment.

Methods: Data from the National Ambulatory Medical Care Survey (NAMCS) for the years 1990 through 1995, for children age five through 18 years were utilized for this analysis.

Results: The number of office-based visits documenting a diagnosis of ADHD increased from 947,208 in 1990, to 2,357,833 in 1995. Between 1990 and 1995, the number of visits by girls diagnosed with ADHD rose 3.9-fold ($p<0.05$), and the mean patient age increased by over one year; from 9.7 in 1990, to 10.8 in 1995 ($p<0.05$). The percentage of office-based visits resulting in a diagnosis of ADHD increased from 1.1% of all visits in this age group in 1990, to 2.8% by 1995. We discerned a 2.3-fold increase ($p<0.05$) in the population-adjusted rate of office-based visits documenting a diagnosis of ADHD; a 2.9-fold increase ($p<0.05$) in the population-adjusted rate of ADHD patients prescribed stimulant pharmacotherapy; and a 2.6-fold increase ($p<0.05$) in the population-adjusted rate of ADHD patients prescribed methylphenidate.

Conclusions: These trends appear partially related to an increasing patient age, and to the fact that girls were increasingly diagnosed with ADHD and treated with stimulant medication during the time-frame 1990 through 1995.

This study was supported by the Pharmacoeconomics and Pharmacoepidemiology Research Unit, College of Pharmacy, Washington State University.

Poster No. 21

Abstract Title: Association of Homozygosity for the Dopamine Transporter with Poor Methylphenidat Response

Authors: Bertrand Winsberg M.D.[1] and David Comings M.D.[2]

1.Brookdale University Hospital and Medical Center
1 Brookdale Plaza ,Brooklyn NY, 11212

2.Department of Medical Genetics, City of Hope Medical Center, Duarte, CA, 91010

Objective: This study attempted to relate the alleles of the D2, D4 and the dopamine transporter to the behavioral outcome of methylphenidate therapy. **Methods**: Children with attention deficit hyperactive disorder were treated with methylphenidate using doses not in excess of 60 mg per day. The drug was incremented until behavioral change was achieved using a decrement in scores of less than one on a commonly used rating scale or until the maximum tolerated dose was achieved. Blood samples were obtained at that point and analyzed for the D2, D4 and dopamine transporter alleles. **Results**: These data were then tested by X^2 to assess the significance of the distribution. Only the dopamine transporter was found to be significant. Homozygosity of the 10 repeat allele was found to characterize nonresponse to methylphenidate therapy (p=.008) (see table 1). **Conclusions:** These findings must be considered as preliminary given the limited sample size. Nevertheless they are encouraging and add support to the possibility that future work will identify not only the basis of clinical response to methylphenidate but also the etiology of some forms of childhood hyperkinesis.

DAT1 Genotype by Responder versus Non-responders

	RESPONDERS	NON-RESPONDERS
10/10 allele	5 (31%)	12 (86%)
9/10: 8/10: 5/9 alleles	11	2

X^2=6.938,df=1,p=.008

Poster No. 22

The Effectiveness and Safety of Combined Treatment with Paroxetine and Clonazepam Compared to Paroxetine Alone for Panic Disorder: Interim Analysis

John J. Worthington, M.D., Naomi M. Simon, M.D., Mark H. Pollack, M.D.,
Patricia C. Marzol, B.A., and Michael W. Otto, Ph.D.
Massachusetts General Hospital, 15 Parkman Street, WAC 812, Boston, MA 02114

Background: In the past few years, the serotonin selective reuptake inhibitors (SSRIs) have become first line treatments of panic disorder. In clinical practice, as many as 50% of patients receiving SSRIs and other antidepressants for panic disorder are concomitantly prescribed benzodiazepines, typically high potency benzodiazepines such as alprazolam or clonazepam. Despite the widespread application of combined antidepressant and benzodiazepine therapy for panic disorder, there has been little systematic assessment of the safety and effectiveness of this strategy in general. Thus, this ongoing study will provide critical information through the first systematic evaluation of the combined pharmacologic treatment strategy for panic disorder, employing a prototypic SSRI, paroxetine, and the high potency benzodiazepine, clonazepam.

Method: The present study is a double-blind, randomized, placebo-controlled, three-arm 12 week trial of 69 patients comparing the efficacy of paroxetine (up to 40 mg/d) combined with clonazepam (up to 2 mg/d), to paroxetine plus placebo in the treatment of patients with panic disorder ± agoraphobia. The clonazepam is administered either a) acutely over 5 weeks and then tapered, or b) maintained during the 12 week course of treatment. In addition, the study examines the safety and tolerability of these treatment strategies including examination of the effects on outcome and emergence of withdrawal symptomatology in patients tapering clonazepam during concomitant antidepressant therapy.

Results: We will present an update on the initial 50 patients randomized to treatment. Primary outcome measures will include the Panic Disorder Severity Scale and CGI-Severity. In addition we will examine adverse effects and tolerability during initiation of treatment and during the benzodiazepine taper period (weeks 5-9). Preliminary analyses of the first 21 patients (71% female, mean age = 35, duration of panic disorder = 10 years) showed that at endpoint with the last observation carried forward method, responder status (CGI-S = 1 or 2 and 0 panic attacks) at week 12 was achieved by 14% of patients on paroxetine plus placebo, 50% on paroxetine plus continued clonazepam, and 65% on paroxetine plus acute phase clonazepam with taper. Drop-out rates in the first three weeks were higher in the paroxetine plus placebo group (43%) compared to the two benzodiazepine groups (7%), suggesting improved tolerability of the combined treatment strategy, although the total number of side effects reported by patients in the first three weeks were similar.

Conclusions: Preliminary analysis of this ongoing trial of combined paroxetine and clonazepam treatment strategies for the treatment of panic disorder suggested improved rates of remission in both the combined treatment groups compared with paroxetine alone at 12 weeks.

Poster No. 23

Methylphenidate Dose-Dependently Decreases Blood Flow in the Cerebellar Vermis of Children with ADHD

Carl M. Anderson, Ph.D.1 , A.M. Polcari, RN., Ph.D.1 , C.E. McGreenery 1 , L.C. Maas, Ph.D 2 .,P.F. Renshaw, Ph.D., M.D 2 ., M.H. Teicher , Ph.D., M.D 1 .

1 Developmental Biopsychiatry Research Program and 2 Brain Imaging Center, McLean Hospital,Department of Psychiatry, Harvard Medical School, 115 Mill Street, Belmont MA 02178.

Recent evidence from animal and human research suggests that developmental pathology of the cerebellum may be particularly relevant to understanding childhood attention deficit hyperactivity disorder or ADHD. For example, Altman observed that selective x-ray irradiation of the cerebellum in infant rats during a critical granule cell migration period results in enduring morphological alterations and a period of behavioral hyperactivity during adolescence which declines in adulthood. Findings from several recent studies employing magnetic resonance imaging-based morphometric analysis of the cerebellum in ADHD children implicate a midline region of the cerebellum called the "inferior posterior lobe" of the vermis in the pathophysiology of motor and cognitive defects (Berquin et al. 1998). Schmahmann has proposed that cerebellar pathology, which typically results in motor dysmetria (the term derived from the Greek (dys) "bad" and (metron) "taking a measure of time and/or space") may also contribute to a "cognitive dysmetria" in adults characterized by defects in the "... speed, capacity, consistency and appropriateness of mental or cognitive processes" (Schmahmann, 1998) -- a description consistent with behavioral deficits observed in ADHD.

Our group used steady-state fMRI to assess resting blood flow in the cerebellar vermis in ADHD (all subtypes) children (6 male, aged 9.93+0.45) assigned to a 4 week double-blind schedule of methylphenidate (one week each of 0.25, 0.4, 0.75mg/kg bid methylphenidate or placebo). An overall dose-dependent resting blood flow decrease in the vermis was observed [$F_{1,5} = 5.261$, $p < .01$].

Trend analysis supported a dose-dependent linear decline in perfusion [$F_{1,5} = 13.676$, $p < .001$].

In summary, cerebellar modulation of the forebrain may be an important element of the neuropharmacology of methylphenidate in childhood ADHD.

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Poster No. 24

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Poster No. 25

Pharmacotherapy of Attention Deficit Hyperactivity Disorder (ADHD) in Psychiatrically Referred Girls

Louise Glassner Cohen, Pharm.D., Joseph Biederman, M.D., Susan Gilson, Pharm.D. Sabrina Whitt, Pharm.D., Jean Frazier, M.D., Janet Wozniak, M.D. Timothy E. Wilens, M.D, Thomas Spencer, M.D., Erick Mick, B.A.

[1]Pediatric Psychopharmacology Clinic and Research Program, Massachusetts General Hospital, WACC 725, Boston, MA02114 and Department of Psychiatry, Harvard Medical School, Boston, MA.

[2] Department of Pharmacy, Massachusetts General Hospital

Background : Attention deficit hyperactivity disorder (ADHD) is the most widely diagnosed and researched neuropsychiatric disorder in children and adolescents. Despite the large number of published trials describing pharmacologic, psychosocial and educational interventions in children with ADHD, there are no data to describe the treatment of ADHD in girls. Recent research suggest that gender-related differences the in neuropsychological function in children with ADHD exist. These differences in function, coupled with developmental and gender-related differences in the pharmacokinetics of medications, may significantly influence the pharmacodynamics of medications in girls with ADHD and ultimately influence patient outcome.

Objective: To describe the pharmacotherapy of ADHD in psychiatrically referred girls.

Methods: Data from a total of 41 girls (33 children and 8 adolescents) referred to the Pediatric Psychopharmacology Unit between 1992 and 1996 for treatment by a board-certified child psychiatrists were retrospectively collected. All diagnostic assessments were based on DSM-III-R structured clinical interview and Kiddie-SADS-E, 4th version. Subjects had a history of lifetime and current ADHD and were treated in the clinic for more than one month.

Results: The subjects were referred to the pediatric psychopharmacology unit for treatment of ADHD and comorbid disorders at a mean age of (mean $\pm$ sd) 9.7 $\pm$ 3.2 years. In addition to ADHD, 14 had major depressive disorder (34%), 17 had ODD (41%), 5 had bipolar II disorder (12%), 21 had one or more anxiety disorders (60%). Of these 28 (65%) received previous drug therapy, 20 (48%) received therapy for ADHD of these 13 (31%) received stimulants. The average length of treatment captured was 646 $\pm$ 503.62 days, 21 (70%) are still treated in the clinic. Combined pharmacotherapy for the treatment of ADHD and comorbid disorders was common. Of the courses of treatment prescribed during the study, 18 (46%) subjects received therapy with only one medication, 27 (65%) received two medications, 18 (43%) received three medications and 6 (15%) received 4 medications. Stimulants were the most frequently used medication, 31 subjects (75%) but were prescribed as monotherapy in only 13 (30%) subjects.

Methylphenidate was prescribed in 31 subjects (75%) up to the maximal dose of 1.18mg/kg (MPH). Clonidine, SSRIs, anxiolytics and mood stabilizers were combined with stimulants to address treatment resistance, to treat comorbid disorders or to treat adverse effects of medications.

Conclusions: In a sample of psychiatrically referred girls with ADHD, combined pharmacotherapy with stimulants and other psychotropic medication is required to address treatment resistance, to treat comorbid disorders or treat adverse effects of medications during long-term therapy.

Poster No. 26

Chronic Stimulant Treatment Effects on Weight Acquistion Rates of ADHD Children

1Laurence L. Greenhill, M.D. for the MTA Cooperative Study Group.

1New York State Psychiatric Institute (NYSPI), 1051 Riverside Drive, NY, NY, 10032.

Background: Although more than 2 million American children are administered daily psychostimulant doses for treatment of Attention Deficit Hyperactivity Disorder (ADHD), the long-term effects of these drugs on children's growth rates remain controversial (ADHD, 1998). Single-site studies of stimulants often report weight changes but have not employed a group of children with ADHD who have been randomly assigned to a no-medication treatment group for over one year of treatment (Gittelman-Klein et al., 1988). Moreover, evaluation of the resulting growth curves has not taken advantage of the increased validity in the statistical model and the increased reliability in measurement offered by random regression analyses of repeated measurements. **Method:** The 6-site, NIMH collaborative Multimodal Treatment Study of Children with Attention Deficit Hyperactivity disorder (MTA Study) recruited and rigorously assessed 579 children with ADHD age 7-9, for a 14 month treatment period, and again at 24 months for follow-up (MTA Cooperative Group, in press). Half this group, or 288 children, were randomized to medication conditions, including medication-only (Medmgt group) (n=144) and combined treatment (CT group) (n=145) groups. The remaining children were randomly assigned to a no-medication behavioral treatment (BT group, N=144) or to treatment in the commmunity (A&R Group, N=144), where 66% were treated with stimulants. Each child was measured for height and weight at baseline, 3 , 9 , 14 (end of treatment), and 24 months (follow-up). **Results:** A repeated measures ANOVA was executed. Gender, treatment assignment, and site were included as between-subjects factors. Main effect for time ($F(1,321)=171.4$, n=579, $p=0.0001$) is significant, group ($F(3,321)=0.79$, n=579, $p=0.5$) is not. Interaction of group by time is significant, ($F(321)=6.65$, n=579, $p=0.0002$. For height, main effect for time ($F(1,320)=1599.08$, n=579, $P=0.0001$) is significant, group ($F(3,320)=1.64$, n=579, $p=0.18$) is not, interaction of group by time is significant, $F(3,320)=7.76$, n=579, $p=0.0001$. Random regression analyses (n=579) confirmed interaction of group by time for weight ($F=10.54$, $P=0.0001$) and for height ($F=6.56$, $P=0.0003$). When compared to the BT group, the Medmgt and A&R groups show decreased rates (kg/year) during the baseline to 14th month interval and parallel (to BT and C groups) weight gain rates during the 14th to 24th month interval. All children achieved linear growth in height throughout the 24 months with no effect of treatment. There was considerable child-to-child variation on the mm/year growth rate parameter. **Significance:** ADHD children treated with stimulants for 14 months gain weight significantly slower than ADHD children randomized to a no-drug behavioral treatment.

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Poster No. 27

Health Care Service System Variations in Youth Psychotropic Treatments for ADHD and Depression

Susan dosReis, B.S., Ph.D. Candidate,[1] Julie Magno Zito, Ph.D.,[2] Daniel J. Safer, M.D.,[3] Karen Soeken, Ph.D.[2]

[1]University of Maryland, 100 N. Greene St., Rm 514, Baltimore, MD 21201
[2]University of Maryland, Baltimore, MD
[3]Johns Hopkins Medical Institutions, Baltimore, MD

Background: Attention deficit hyperactivity disorder (ADHD) and depression are commonly diagnosed psychiatric disorders among youths, and psychotropic treatments for these mental health problems have increased dramatically in the past decade. However, population-based information on psychotropic treatment patterns across health care systems is sparse. This study compares population-based psychotropic treatment for youths with ADHD and depression so as to assess the impact of health care system and provider specialty on clinical prescribing patterns.

Methods: The study is a retrospective, cross-sectional analysis of psychotropic prescription patterns for youths enrolled in a staff-model health maintenance organization (HMO) and in a state Medicaid program. Youths less than 20 years old with a psychiatric diagnosis or a psychopharmacologic prescription during the calendar year 1996 were selected from a large populous county in a Mid-Atlantic state. The data include the youth's age, gender, continuous enrollment status, clinical diagnoses, and prescription medications as well as the provider's specialty. Multivariate logistic regression models will examine the influence of the health care system (managed care versus Medicaid) and provider specialty (mental health versus non-mental health) on psychotropic treatments for youths with (a) an ADHD diagnosis and (b) a depression diagnosis, while controlling for the youth's age, gender, and geographic locale.

Results: Findings from the univariate analyses indicate that the prevalence of an ADHD diagnosis alone was 2-fold higher among HMO male youths (4.8%) compared to male Medicaid youths (1.96 %) and 3-fold higher among the female HMO sample (1.35%) compared to the female Medicaid group (0.46%). This disparity by gender and health care system was not observed for youths with a diagnosis of depression. Youths aged 15-19 years in the HMO population were more likely to be diagnosed with ADHD (2.01%) compared to 15-19 year old Medicaid youths (0.37%). These adolescents were also more likely to have a diagnosis of depression in the HMO sample (2.18%) compared to the Medicaid adolescents (1.6%). Among youths with a sole diagnosis of ADHD, a 3-fold higher prevalence in the HMO compared to the Medicaid sample was observed for stimulants (2.43% versus 0.79%) and alpha-agonists (0.32% versus 0.1%). Psychotropic treatments for children with a sole diagnosis of depression did not differ according to health care system. Nearly 80% of the HMO youths with a diagnosis of ADHD and 45% with a diagnosis of depression received psychotropic medications compared to 74% and 32%, respectively, for the Medicaid youths. Comparing the diagnostic prevalence

according to provider specialty, the data show that ADHD was more likely to be treated by a non-mental health provider and depression was more likely to be treated by mental health specialists. Non-mental health services for ADHD were more than 2-fold higher in the HMO population (1.97%) compared to the Medicaid population (0.79%). Comparisons among children with depression did not differ by health care system or provider specialty. Stimulant use was more than 2-fold higher among non-mental health providers for both HMO and Medicaid youths. Additional findings from logistic regression analyses will be presented.

Implications of the Findings: The preliminary findings reveal sizable health care system and provider specialty variations in the treatment of childhood ADHD. Knowledge of the fundamental differences across populations and health care service systems is necessary so that the clinical treatment of ADHD will incorporate the individual needs of these youths.

Funding Source: Dissertation Fellowship Award 5-R03-MH58470-01A1

Poster No. 28

Acoustic Startle and Prepulse Inhibition in Attention Deficit Disorder

Lenard A. Adler, M.D.[1], Erica Duncan, M.D.[2,] Arthi Parwani, M.D. [2], Michael Kunz, M.D.[2], Toby Efferen, M.S.[2], Subhajit Chakravorty, M.D.[2], Sandor Szilagy, B.S.[2], Steven Madonick, M.D.[2,] Rajive Rajan, M.D.[2],

Stephen Gonzenbach, Ed.D.[2], John Rotrosen, M.D[2].

[1]New York VAMC/NYU School of Medicine, Psychiatry 116A, 423 E. 23 Street, New York, NY 10010.
[2]New York VAMC/NYU School of Medicine, New York, NY.

Background: Attention deficit disorder (ADD) is a behavioral disorder which has been linked to dysfunction of dopaminergic and noradrenergic circuits. Treatment with stimulants often leads to a diminution of symptoms. The acoustic startle response is mediated by a simple subcortical four-synapse circuit; the response is inhibited by the presence of a weak, nonstartling prestimulus (prepulse inhibition, PPI). Modulatory inputs to the circuit from several neuroanatomic loci render the startle response and PPI sensitive to pharmacologic manipulation, notably by agents with dopaminergic activity. PPI has been used as a physiologic probe of dopaminergic function. Because of the overlap of anatomic sites and neurotransmitters implicated both in ADD and in the modulation of the startle circuit, we hypothesized that acoustic startle and PPI might be abnormal in ADD subjects, and that treatment would alter the abnormality.

Design: 23 ADD subjects off stimulants were compared to 23 age- and sex-matched normal controls in a paradigm which tested startle reactivity and PPI. 14 of these subjects with ADD were tested both off and then on stimulant treatment. The ADD subjects were either untreated for at least six months prior to initial testing and retested after clinical stabilization on stimulant treatment (N=11), or were tested initially prior to their AM stimulant dose, and again one to ten weeks later after having taken their morning stimulant dose (N=12).

Subjects: A diagnosis of ADD was confirmed in the patient group by the Wender Utah Rating Scale and the Attention Deficit Hyperactivity Questionnaire; all subjects met DSM IV ADD criteria. All subjects were screened to exclude any active Axis I disorder other than ADD in the patient group. A separate group of 14 normals served as statistical controls for the test-retest design.

Methods: The eyeblink component of the startle response was quantified by means of EMG recording of the right orbicularis oculi muscle. Startle response and PPI were assessed in a paradigm consisting of 72 trials over 30 minutes.

Results: *1. ADD vs Normals:* In the between group design, 23 ADD subjects had greater startle amplitudes and greater PPI than 23 matched normals in all conditions across the test session,

although these differences failed to reach statistical significance (F[1,44]=1.59, p=.2). *2. Treatment effect in ADD subjects:* The 14 untreated ADD subjects had a significant decline in the amplitude of startle to the pulse alone condition after stimulant treatment (F[1,13]=4.85, p=.05). Stimulant treatment was also associated with a significant decrease in PPI (F[1,13]= 12.40, p=.004). A comparison group of 16 normal statistical controls tested sequentially failed to demonstrate any change in amplitude of startle response nor in PPI, indicating that the change in the ADD subjects was not due to the test-retest design.

Conclusions: ADD subjects had nonsignificantly greater startle amplitude and PPI than normals. There were significant decreases in startle amplitude and in PPI as a biological concomitant to stimulant treatment in 14 ADD subjects, leading to a normalization of these measures. This finding is consistent with the increase in dopaminergic neurotransmission occurring in stimulant treatment, and may reflect changes in dopamine levels in areas which modulate the startle circuit.

Supported: in part by the Department of Veterans Affairs and NYU School

Poster No. 29

Health Care Service System Variations in Youth Psychotropic Treatments for ADHD and Depression

Susan dosReis, B.S., Ph.D. Candidate,[1] Julie Magno Zito, Ph.D.,[2] Daniel J. Safer, M.D.,[3] Karen Soeken, Ph.D.[2]

[1]University of Maryland, 100 N. Greene St., Rm 514, Baltimore, MD 21201
[2]University of Maryland, Baltimore, MD
[3]Johns Hopkins Medical Institutions, Baltimore, MD

Background: Attention deficit hyperactivity disorder (ADHD) and depression are commonly diagnosed psychiatric disorders among youths, and psychotropic treatments for these mental health problems have increased dramatically in the past decade. However, population-based information on psychotropic treatment patterns across health care systems is sparse. This study compares population-based psychotropic treatment for youths with ADHD and depression so as to assess the impact of health care system and provider specialty on clinical prescribing patterns.

Methods: The study is a retrospective, cross-sectional analysis of psychotropic prescription patterns for youths enrolled in a staff-model health maintenance organization (HMO) and in a state Medicaid program. Youths less than 20 years old with a psychiatric diagnosis or a psychopharmacologic prescription during the calendar year 1996 were selected from a large populous county in a Mid-Atlantic state. The data include the youth's age, gender, continuous enrollment status, clinical diagnoses, and prescription medications as well as the provider's specialty. Multivariate logistic regression models will examine the influence of the health care system (managed care versus Medicaid) and provider specialty (mental health versus non-mental health) on psychotropic treatments for youths with (a) an ADHD diagnosis and (b) a depression diagnosis, while controlling for the youth's age, gender, and geographic locale.

Results: Findings from the univariate analyses indicate that the prevalence of an ADHD diagnosis alone was 2-fold higher among HMO male youths (4.8%) compared to male Medicaid youths (1.96 %) and 3-fold higher among the female HMO sample (1.35%) compared to the female Medicaid group (0.46%). This disparity by gender and health care system was not observed for youths with a diagnosis of depression. Youths aged 15-19 years in the HMO population were more likely to be diagnosed with ADHD (2.01%) compared to 15-19 year old Medicaid youths (0.37%). These adolescents were also more likely to have a diagnosis of depression in the HMO sample (2.18%) compared to the Medicaid adolescents (1.6%). Among youths with a sole diagnosis of ADHD, a 3-fold higher prevalence in the HMO compared to the Medicaid sample was observed for stimulants (2.43% versus 0.79%) and alpha-agonists (0.32% versus 0.1%). Psychotropic treatments for children with a sole diagnosis of depression did not differ according to health care system. Nearly 80% of the HMO youths with a diagnosis of ADHD and 45% with a diagnosis of depression received psychotropic medications compared to 74% and 32%, respectively, for the Medicaid youths. Comparing the diagnostic prevalence

according to provider specialty, the data show that ADHD was more likely to be treated by a non-mental health provider and depression was more likely to be treated by mental health specialists. Non-mental health services for ADHD were more than 2-fold higher in the HMO population (1.97%) compared to the Medicaid population (0.79%). Comparisons among children with depression did not differ by health care system or provider specialty. Stimulant use was more than 2-fold higher among non-mental health providers for both HMO and Medicaid youths. Additional findings from logistic regression analyses will be presented.

Implications of the Findings: The preliminary findings reveal sizable health care system and provider specialty variations in the treatment of childhood ADHD. Knowledge of the fundamental differences across populations and health care service systems is necessary so that the clinical treatment of ADHD will incorporate the individual needs of these youths.

Funding Source: Dissertation Fellowship Award 5-R03-MH58470-01A1

Poster No. 30

Effectiveness and Tolerability of Adderall in Adults with Attention Deficit Hyperactivity Disorder

T. Spencer, M.D.[1] ; T. Wilens, M.D.[2] ; J. Biederman, M.D. [2]; J. Kagan, BA[2]; Sarah Kate Bearman, BA[2].

[1] Massachusetts General Hospital, Pediatric Psychopharmacology Unit, 15 Parkman St. WACC 725, Boston, MA. 02114
[2] Boston, MA

Background

In recent years, evidence has been accumulating that the syndrome of attention deficit-hyperactivity disorder (ADHD) frequently persists into adulthood and is associated with high rates of academic and work failure. The literature shows that Adult ADHD can be reliably diagnosed and that the diagnosis confers considerable power to forecast future course, complications and treatment response. In addition, there is mounting evidence for genetic transmission, specific treatment responses, and abnormalities in brain structure and function in affected individuals. Thus, the available literature provides converging evidence that adult ADHD is a valid clinical diagnosis. Despite the increasing recognition that children with ADHD commonly grow up to be adults with the same disorder, little is known about the treatment of this disorder in adults. Amphetamines have been used for over 60 years with proven efficacy in child and adolescent attention deficit-hyperactivity disorder (ADHD) (N=22 studies, 1,140 patients), but have never been tested in a controlled trial in adult ADHD. Adderall is a racemic mixture of mixed salts of dextro and levo amphetamine with a long half-life of 8 to 12 hours. Usage data suggest that this amphetamine formulation may have an especially advantageous side effect profile and be effective in once or twice daily dosing.

Method

This was a randomized, 7-week placebo-controlled crossover study of amphetamine in adult (N=23) patients with DSM-IV ADHD using standardized instruments for diagnosis, separate assessments of ADHD, depressive and anxiety symptoms. Study medication was titrated up to 20 mg/day by week one (10 mg B.i.D.), 40 mg/day (20 mg B.i.D.) by week two and 60 mg/day (30 mg B.i.D.) by week three unless adverse effects emerged. Improvement was defined as a reduction in the ADHD rating scale of $\geq$ 30% and much or very much improved on the Clinician's Global Impression Scale.

Results

We are reporting preliminary results on the first 23 patients. Amphetamine was well tolerated and effective. There was a very significant drug by time interaction for ADHD symptoms. Using

a pre-established definition of improvement, there was a higher response rate for ADHD symptoms during (74% vs. 0%; $p<0.001$; amphetamine vs. placebo treatment respectively).

Conclusion

Though preliminary, our data demonstrate a robust response for ADHD adults consistent with that seen in ADHD children. Although our design did not permit the separation of dose and time effects, our data suggest that adults require robust dosing to attain adequate clinical response. Furthermore, our adults readily tolerated a robust dose.

Funding Source

Funding for this study was provided by Shire Laboratories Inc.

Poster No. 31

Screening for Burden of Illness of Depression and Other Chronic Conditions in African-American Primary Care Centers.

DiAnne Bradford, Ph.D.[1], Shakoora Rashada, M.D.[2], Lonnie Fuller, M.D.[2]

Departments of Psychiatry[1] and Family Medicine [2], Morehouse School of Medicine, 720 Westview Dr. SW, Atlanta, GA 30310-1495, *e-mail: Bradford@msm.edu*

Ethnic scholars have long argued that conceptual models, diagnostic tools and treatment approaches are inadequate in identifying, diagnosing and effectively treating psychiatric disorders in African Americans. African Americans have consistently been over-diagnosed with schizophrenia and under-diagnosed with depression (Adebimpe, 1984) but little empirical evidence exists of either greater prevalence or greater vulnerability to depression (Myers, 1993). There is an indication that African Americans may report depression in more somatic symptoms than dysphoric mood. This has been supported by one study using both the SF-36 and the HAM-D (Brown et al., 1996). The first step in determining potential racial/ethnic differences in the reporting of depressive symptoms was to establish the prevalence of depression within an African American primary care community, and assess the impact on the physical and mental components of the SF-36. The aims of this pilot study were to:

1. determine the percentage of patients within this population with chronic medical conditions, including depression
2. determine the impact of each chronic condition on each health measurement, the physical and the mental components of the SF-36
3. relate the impact/burden of illness of those with chronic conditions compared with those with no chronic condition within this study, and make a comparison with historical data of majority norms with similar conditions.

Five hundred and thirty (530) adults clients were approached for participation in the trial from two primary care centers in southeast Atlanta; 430 agreed to participate (77%) and gave consent and completed the SF-36. Among the most common reasons for refusal were: lack of interest and lack of time. There were 401 African American participants, 14 Caucasians and one Native American. Race/ethnicity could not be determined for 15 participants. Only the initial analysis for the identified African American cohort will be presented (N = 401). The average age of the cohort was 43 years (range:18 - 84 years). Women represented 77% of the cohort, men, 23%. There was no evidence of selective refusal of participation by the male cohort approached. 31% were married, 74% were insured; 51% of the cohort earned $20,000 or less.

The most commonly reported chronic disorders determined by chart reviews were: hypertension (30%), followed by chronic back problems (18%), arthritis (14%) and diabetes (10%). Seventeen patients (4%) had "depression" given as a diagnosis in their patient chart. Patients with arthritis showed the most disability in the physical components of the SF-36, and

those with depression had the greatest impact on the mental components. However, patients with depression also showed significant disability measured on the physical components, similar to patients with angina.

These preliminary data suggest an under diagnosis of depression in African American primary care centers, and a significant impact on both physical and mental elements of quality of life and burden of illness. Using a within group design across diverse centers with regard to insurance status, income, education, and overall health status, risk factors within the African American community can be identified. Identifying factors associated with high risk for depression in African Americans will lead to interventions to identify and treat individuals, thereby reducing morbidity and mortality, which will have major public health implications.

Supported by an unrestricted grant from Merck & Co, and RCMII grant 1P20RR11104

Poster No. 32

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Poster No. 33

More Sites or More Time?: Approaching Optimal Enrollment Strategies in Multi-site Clinical Trials

Richard Landin, PhD, Todd A. DeVries, Ph.D, David J. Debota, MD, and Mark A. Demitrack, MD

Antidepressant Clinical Development, Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285

INTRODUCTION: The design and logistical configuration of multisite clinical trials is a deceptively complex process. In the study of antidepressant and antianxiety medications, the observed clinical treatment effect as determined by validated indices of symptom change, is typically modest in size, with a considerable variability in its measurement (Demitrack, et al, 1998). As a result, large sample sizes are required to achieve an acceptable level of statistical power. At the same time, the increasingly competitive drug development environment mandates the timely completion of clinical trials. Prompt enrollment of a sufficient number of subjects is, therefore, of utmost interest. Whether to achieve a particular enrollment target by increasing the number of sites or the number of patients per site is an enduring logistical problem. In this report, we describe a comprehensive retrospective examination of 9 large multisite clinical trials which included the study of fluoxetine and placebo. We hypothesized that increasing numbers of patients per site would be associated with an increasing likelihood of demonstrating the expected difference between active drug and placebo.

METHODS: 9 multisite clinical trials were included in this analysis. The 17-item Hamilton Depression Rating Scale was used as the primary outcome measure to assess baseline to endpoint clinical change in patients meeting DSM-III, IIIR, or IV criteria for major depression. Although some trials included more than two treatment arms, the treatment difference between the placebo and fluoxetine comparator arms was considered as an index of clinical trial outcome. Sites were stratified according to the aggregate number of patients recruited.

RESULTS: Pairwise comparison of the average treatment difference between fluoxetine and placebo revealed a stepwise and orderly increase in accordance with the increase in number of patients per site. In addition, simulations from the data suggest that the variability across small sites is consistent with the variability across large sites which, in turn, suggests that the stepwise increase in treatment effect is an issue of bias and cannot be resolved by simply increasing the number of small sites.

DISCUSSION: Reducing variability, enhancing precision and timely implementation of multisite clinical trials is an ideal. All too often, rapid enrollment is viewed as a primary goal to be achieved at all costs, without thoughtful consideration of the implications of the various methods used to achieve that goal. To that end, the results we report here emphasize the importance of a

proper balance between speed of enrollment and optimal site configuration in the design of multisite clinical trials.

Reference:

Demitrack, M.A., Faries, D., Herrera, J.M., DeBrota, D.J., Potter, W.Z.: The Problem of Measurement Error in Multisite Clinical Trials. Psychopharmacololgy Bulletin 34(1):19-24, 1998

Poster No. 34

Fast Facts From Free Memory Screenings Conducted in the Greater New Orleans Area September, 1998

Bee Pollock, B.S.[1]

[1] Department of Psychiatry and Neurology, Tulane University Medical Center, 1430 Tulane Avenue, New Olreans, LA 70112

Five free memory screenings were conducted in the greater New Orleans Area, September 22-25, 1998, as a public service. The goal was to increase public awareness of memory disorders, including dementias, the importance of early diagnosis and treatment. It was good public relations for the facilities involved and "Not commercial", no advertising appeared on the result slip given to patients to take to their physicians. Different sites and times were used to encourage participation. Tulane University Hospital & Clinic's 800 number was used for participants to preregister to get attendance numbers. Tulane University Hospital & Clinic, Lakeland and Lakeview Hospitals, DePaul Tulane Behavioral Health Center and West Jefferson Behavioral Health Center were very gracious in donating use of their facilities for this endeavor. At each site, a neurologist gave a 15 minute talk: "What is memory disorder and various causes of memory loss. " Afterwards, those who wished to take the MMSE were directed to MMSE testing areas. The result slip given to the patient had *" Please take this result slip to your doctor. He/She will discuss the meaning of the results with you."* Light refreshments were served.

SITES /TIMES: Tulane University Hospital and Clinic located downtown, in the medical center complex, and is affiliated with Tulane University School of Medicine. Lakeland Hospital is located approximately 20 minutes from downtown. in eastern New Orleans. West Jefferson Behavioral Health Center is located across the Mississippi River on the West Bank,. DePaul*Tulane Behavioral Health Center is located in uptown New Orleans, near Tulane and Loyola Universities and Audubon Park. Lakeview Hospital is in Covington, 45 miles from New Orleans across Lake Pontchartrain. TIMES: 9-11 a.m., West Jeff and Lakeview; 11 a.m.-1 p.m, Tulane; and 2-4 p.m., Lakeland and DePaul*Tulane. All but Tulane had free parking.

REFERRAL SOURCES: **TV**: an 8 minute interview on the Medical News segment of WWL-TV, the local CBS affiliate and was **free** as part of the Medical News. This aired 7:22-7:30 a.m. the morning of the first event, with the 800 number, dates and times shown. A **4x6 ad ran 3 times** in the local newspaper, Thursday and Sunday preceding the first event and Thursday morning, with 3 events pending, **cost $2100**. 8% of those screened were referred by support groups/4 and by the speaker/2.

FAST FACTS: 109 attended. **79 screened: 81% responded to TV,** 11% newspaper ad, 8% other. Demographics of 79 **SCREENED**: **25 males /33%, 76 females/ 67%.** 79 screened, 76 demographic information available, 3 forms inadvertently given to patients. **Hormone**

replacement therapy: 43% yes, 57% no. **Ages 61 to 80: 19/25 males and 30/51 females. MMSE scores: 29-30: 72%; 26-28: 15%;** 19-25: 11%; <18: 1%.

Suggestions for future events: use shopping malls, church and school settings to take away the "hospital" image and broaden community involvement and community area.

Pfizer/EISAI provided MMSE forms and refreshments. Tulane University Hospital & Clinic paid for the ad.

Poster No. 35

PLACEBO RESPONSE IN DEPRESSION STUDIES: DO PREVIOUSLY REPORTED PREDICTORS HAVE ANY UTILITY?

Charles Wilcox, Ph.D.[1]; Francine Cho, B.A.[1]; Jon Heiser, M.D.[2]; Judy Morrissey, R.N., M.S.N.[3]; Barbara Katz, R.N.[4]; Daniel Grosz, M.D.[3]; and Don DeFrancisco, M.D., Ph.D.[4]

[1] Pharmacology Research Institute, 10691 Los Alamitos Boulevard, Suite 101, Los Alamitos, CA 90720-2149
[2] Pharmacology Research Institute, Riverside, CA
[3] Pharmacology Research Institute, Northridge, CA
[4] Pharmacology Research Institute, Newport Beach, CA

The pervasive problem of seemingly unpredictable placebo response rates in studies involving both investigational and marketed antidepressant medications is common knowledge--within the industry. A number of researchers, including members of our group, have previously reported on *potential* predictors of placebo response. A key question has been, are any of these purported predictors really valid and reliable? Or, are these prior reports merely chance findings which are not replicable? Having a database from several recent depression trials, involving patients fulfilling DSM-IV criteria for major depressive disorder, we analyzed data for 207 patients (96 males and 111 females) who were randomly assigned to placebo under double-blind conditions. Five variables were retrospectively analyzed: 1) the duration of treatment; 2) the number of concomitant medications being taken at screen; 3) the number of medical conditions reported at screen; 4) marital status, and 5) gender. For four out of five variables, statistically significant differences were observed:

- The number of days on placebo was positively correlated with the likelihood of a positive response to placebo $p < .01$.
- The number of concomitant medications being taken at screen was positively correlated with placebo response $p < .05$.
- One's marital status strongly correlated with placebo response, with married patients appearing to be roughly twice as likely as separated/divorced patients to respond positively to placebo $p < .05$.
- As in prior analyses, our results indicated that gender was associated with placebo response. Whereas nearly 40% of the women were placebo responders, only 21% of the males were categorized as positive placebo responders $p < .005$.

The number of medical conditions reported at screen did not demonstrate statistically significant evidence of being positively correlated with placebo response, although there was a trend in that direction ($p = .057$). A number of other variables, such as baseline HAM-D scores and age were also analyzed and those results will be presented as well. These findings are consistent with

previously published reports. Their implications for the design of future studies, as well as the interaction with and treatment of research subjects will be presented.

Funding for this retrospective study, including all statistical analyses, was provided (internally) by Pharmacology Research Institute.

Poster No. 36

A Review of Placebo-Controlled Efficacy Trials for Antidepressants as Evaluated by the FDA

Kalyan Ghosh, Ph.D.[1] and Mark S. Kramer, M.D., Ph.D.[2]

[1,2] Merck & Co. Inc., BL3-2, P.O.Box 4, West Point, PA 19486

We summarize the trial designs, sample baseline characteristics, and overall outcomes of 60 placebo-controlled depression trials of 7 drugs (Fluoxetine, Paroxetine, Venlafaxine, Nefazadone, Mirtazapine, Sertraline and Citalopram), as contained in FDA approval packages obtained through Freedom of Information. Typically these trials were 4 to 8 weeks in duration and the HAM-D score was the primary efficacy variable; other metrics, such as the HAM-D "depressed mood" item, CGI severity and CGI improvement scores were also included in the studies.

Our review suggests that:

1. There is a high correlation among various outcome measures in each study (i.e., the HAM-D total score is very much representative of the outcomes obtained with other metrics (e.g., CGI, HAM-D item #1).

2. Among the factors contributing to the failure of a study the most important was the level of placebo response; this was indirectly related to the severity of illness of the sample at baseline (most studies enrolling patients with HAM-D21 baseline severity of ≥ 26 were successful). In some cases, point estimates of the difference between active and placebo treatments were often similar for positive v. non-positive studies, with small sample size generally contributing to the latter outcome. Surprisingly, the least important factors were 1) the variability of the primary measure and 2) whether or not the study was conducted at a single v. multiple sites.

Thus, to minimize the proportion of failed trials the conduct of antidepressant trials must primarily be aimed at reducing placebo response rates. Based on our review, only patients with an "adequate" severity of depression (i.e., less likely to respond to placebo, and more likely to respond to active treatment) should be enrolled in such trials. The entry scores on the HAM-D17 of about 22 should be sufficient, providing such patients are truly ill. Though baseline depression severity can be psychometrically stipulated, it cannot except by cumbersome devices be absolutely standardized/objectified. Thus, principal investigators must consciously implement a rigorous professional standard of enrolling in such trials only those patients (i.e., adequately depressed) who in their opinions are likely to provide informative outcomes. Sponsors and

principal investigators should frankly discuss the type of data presented herein prior to conducting studies.

Poster No. 37

Differences Between Drop-outs And Completers In The Continuation Phase Of A Clinical Trial

Shamsah Sonawalla, M.D.,[1] Amy Farabaugh, M.A.,[2] Vinita Leslie, M.A., Joel Pava, Ph.D., John Matthews, M.D., Maurizio Fava, M.D.

[1]Depression Clinical and Research Program, Massachusetts General Hospital, Harvard Medical School, WACC 812, 15 Parkman Street, Boston, MA 02114

[2]Depression Clinical and Research Program, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Objective: The purpose of this study was to assess the differences between drop-outs and completers, and differences between early and late drop-outs in the continuation phase of a clinical trial. Methods: We studied 119 outpatients who were treatment responders in an 8-week open trial with fluoxetine 20 mg/day and who were then enrolled in a 26-week continuation clinical trial comparing the efficacy of fluoxetine versus fluoxetine and cognitive behavior therapy (CBT). Patients were assessed using the Structured Clinical Interview for DSM-III-R-axis I (SCID-Patient Edition) and axis II disorders (SCID-II), Hamilton Depression Rating Scale (HAM-D-17) and the following self-rated scales: Beck Depression Inventory (BDI), Beck Hopelessness Scale (BHS), Anxiety Sensitivity Inventory (ASI) and the Symptom Questionnaire (SQ) prior to starting the 26-week continuation phase. Results: Eighty-three patients (70%) (46 women and 37 men) completed the study and 36 patients (30%) (16 women and 20 men) dropped out. Mean age of completers was 42.1± 9.0 years and that of drop-outs was 36.1± 11.1 years ($p<0.01$). Younger age was the only statistically significant predictor of dropping-out, although there was a statistical trend for drop-outs to have higher scores on the ASI compared to completers, after adjusting for age ($p=0.06$). Eleven (30.5%) of the 36 patients dropped out early (defined as within the first two-weeks), and 25 patients (69.5%) dropped out later during the continuation phase. There was no significant age difference between early and late drop-outs, nor between early drop-outs and completers. Early drop-outs had significantly higher scores ($p<.01$) compared to completers and late drop-outs on the BDI at the beginning of the continuation phase. On the SQ-depression subscale, early drop-outs had significantly higher scores ($p<.05$) compared to completers at the beginning of the continuation phase. We also found that early drop-outs had significantly higher scores on the BHS and ASI at the beginning of the continuation phase compared to completers. Conclusions: Our data suggest that age is a significant predictor of dropping out of long-term clinical trials. Further, early drop-outs were more depressed, hopeless, and had higher anxiety sensitivity compared to completers, and were more depressed and had higher anxiety sensitivity compared to late drop-outs.

Study supported by NIMH grant # R01-MH-48-483-05

Poster No. 38

Naturalistic Follow-Up of Chronically Depressed Patients Who Discontinued a Double-Blind Trial Compared with Patients Remaining in the Trial

Alan Gelenberg, M.D., Pedro Delgado, M.D., Jan Fawcett, M.D., Robert Hirschfeld, M.D., Mukesh Patel, and Martin Keller, M.D.

635 patients with chronic major depression (>2 years duration) or "double depression" (current major depression superimposed on dysthymia) were randomized to double-blind treatment with sertraline or imipramine in a multicenter three phase trial of acute, continuation, and maintenance treatment. 316 patients completed the continuation phase (7 months) of treatment with either sertraline (50-200 mg daily) or imipramine (50-300 mg daily). Patients who discontinued for a variety of reasons before completing the 7 months of acute and continuation treatment were discharged to obtain further treatment as desired in their communities and were assessed at 6-month intervals in a naturalistic follow-up study. The naturalistic follow-up assessments were identical to the assessments completed for patients who continued in the double-blind trial and included the Hamilton Depression Rating Scale (HDRS), CGI, Social Adjustment Scale (SAS), MOS Health Questionnaire (SF-36) and Longitudinal Follow-Up Evaluation (L.I.F.E.). Most patients included in the trial had suffered from depression for prolonged periods (average of 8 years) at entry to the trial, but the majority had received either inadequate or no pharmacotherapy for depression prior to study entry. The objective of this study was to assess the outcome of this group of chronically depressed patients, comparing those who discontinued with those remaining in the double-blind study conducted in psychiatric research centers.

Results: Patients who continued in the trial had significantly greater improvement in both depressive symptoms and psychosocial functional outcome. Mean HDRS change from baseline was –17.8 for the patients who completed the continuation phase of the double-blind trial compared with a change from baseline in HDRS of –11.0 for the naturalistic follow-up group ($p=0.001$). Similar differences were shown for the change from baseline in SAS scores (-0.70 vs. –0.29; $p=0.01$). Remitter rates (defined as a HDRS ≤ 7 and a CGI ≤ 2) were 63.0% for those who remained in the trial compared with 35.5% for the naturalistic follow-up group ($p=0.001$). Reasons for discontinuation and treatment after discontinuation will be presented as well as data comparing both groups for the other assessments. Conclusion: Appropriate and continued pharmacological treatment of chronic depression resulted in significantly better symptomatic and functional outcome than the level of treatment obtained in the community after discontinuation.

Poster No. 39

The Utility of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) in the Identification of a Homogenous Population of Patients with Major Depressive Episode

Robert A. Massing[1], David J. DeBrota M.D.[2], John H. Herrera, Ph.D.[2], Mark A. Demitrack, M.D.[2], and William Z. Potter, M.D., Ph.D.[2]

[1]Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285

[2]Eli Lilly and Company, Indianapolis, IN

Marketed antidepressants often fail in clinical trials to demonstrate superiority over placebo. Among possible reasons for the high rate of "non-positivity" of trials are the inclusion of patients in studies for whom the diagnosis of major depressive episode (MDE) is not appropriate, and the inclusion of patients in studies with significant psychiatric comorbidity in addition to depression. Especially when a small study is performed, allowing even a few patients into the study population who are likely to be unable to discriminate an "active drug" from a placebo may suffice to render the study uninformative. A great deal of attention has therefore been placed on diagnostic rigor and purity, such that many studies have demanded that patients not only have depression in the judgment of a clinician, but also meet carefully chosen diagnostic criteria as determined in a structured interview such as the SCID. We report on an effort to evaluate the quality and value of the information generated by the application of the SCID in a multicenter antidepressant clinical trial.

METHODS: A total of 319 patients entered an antidepressant trial at 8 sites in the United States between January 1997 and February 1998. Only patients who seemed likely (prior to in-depth evaluation) to be diagnosed with MDE were to have been entered. A SCID was to be completed at the initial visit. A total of 309 SCID's, completed by one of a total of 19 diagnosticians, were collected and all data elements entered into a database. Ten SCID's were either not performed or could not be located for review. Each data element was examined individually to determine the frequency with which (1) a valid response was available when a response should have been available, (2) a valid response was inappropriately missing, or (3) a response was missing because the logic of the SCID items dictated that it should be missing. For each patient, a careful consideration of SCID data was made to determine if the patient (1) met diagnostic criteria for MDE and/or (2) met diagnostic criteria for any other psychiatric disorder.

RESULTS: SCID data elements were only rarely inappropriately missing. Overall, the complex adaptive sequence of items of the SCID was successfully navigated by interviewers in 301 of 309 (97%) of administrations. The SCID data elements were consistent with the diagnosis of MDE in 306 of 309 (99%) of administrations. The diagnosis of MDE was inconsistent with SCID data elements in only 3 patients, 2 of which were subsequently randomized in the study. The SCID data suggested that psychiatric comorbidity was present in 21 patients (3 had GAD, 6 had Panic Disorder, 4 had PTSD, 2 had OCD, 3 met criteria for Social Phobia, 4 met criteria for

manic episodes), of which only 1 patient (with recent panic attack) was subsequently randomized in the study.

CONCLUSIONS: The SCID was effectively administered in this multicenter clinical trial, and generated data of acceptable quality. The application of the SCID in this trial resulted in a number of patients being entered but not subsequently randomized who might otherwise have been randomized. The study's randomized population was thus made more homogenous, in that randomized patients could be confidently said to have MDE and to lack significant psychiatric comorbidity.

Poster No. 40

A Comparison between Interactive Voice Response System-Administered HAM-D and Clinician-Administered HAM-D in Patients with Major Depressive Episode

David J. DeBrota M.D.[1], Mark A. Demitrack, M.D.[2], Richard Landin, Ph.D.[2], Kenneth A. Kobak, M.D.[3], John H. Greist, Ph.D.[3], and William Z. Potter, M.D., Ph.D.[2]

[1]Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285

[2]Eli Lilly and Company, Indianapolis, IN

[3]Healthcare Technology Systems, LLC, Madison, WI

A multicenter study was undertaken to compare the efficacy of an experimental pharmacotherapy with that of placebo and of fluoxetine 20 mg daily in the treatment of patients with major depressive episode. Patients were evaluated at weekly visits with the 17-item Hamilton Depression Scale (HAM-D). The HAM-D was administered both by clinicians conducting structured interviews (SIGH-D, Williams (1988)) and by an interactive voice response (IVR) system with which patients communicated via telephone (Kobak (NCDEU, 1998)). Clinician and IVR HAM-D items and totals were compared at multiple timepoints (visits) to determine the degree of concordance between the administrations.

Patients were evaluated at Visit 1, but not started on study drug until Visit 2, approximately 7 days later. To continue in the study beyond Visit 1, a patient's clinician-rated HAM-D 17-item total (HAMD17c) had to be ≥ 20. To continue beyond Visit 2 (be given study drug), HAMD17c again had to be ≥ 20. Subsequent to Visit 2, there were no requirements for HAMD17c to be at or above a threshold. At no point was any clinician aware of any IVR HAM-D results, and IVR HAM-D 17-item total (HAMD17p) was not used to make continuation/discontinuation decisions.

RESULTS: At a total of 2,252 visits made by a total of 291 patients, both clinician and IVR HAMD data were available for comparison. The entry/continuation criteria applied to HAMD17c but not to HAMD17p at Visits 1 and 2 resulted in significantly different distributions of these scores at these visits. For example, at Visit 1, HAMD17c did not appear normally distributed and only 4 HAMD17c values were < 20, while HAMD17p did appear normally distributed and 110 HAMD17p values were < 20. Mean (± SEM) HAMD17c at Visits 1 and 2 was 22.5 (± 0.1) and 22.3 (± 0.2), respectively, while corresponding values of HAMD17p were 20.9 (± 0.3) and 20.5 (± 0.4). Clinician and IVR HAM-D's at later visits were more concordant than at Visits 1 and 2. For example, at Visit 9, which took place an average of 50 days after Visit 2, mean (± SEM) HAMD17c was 12.0 (± 0.5) and mean (± SEM) HAMD17p at Visit 9 was 11.3 (± 0.6).

CONCLUSIONS: The results suggest that when a patient's clinician-rated severity must be at or above a threshold minimum for the patient to continue in the study, the clinician-rated severity may be inflated compared to the patient-rated severity. Agreement between patient-rated and clinician-rated HAM-D's improves with time, possibly because (1) the severity rating-distorting effects of entry/continuation criteria fade once no longer being applied, (2) clinicians learn to better agree with patients as to severity after repeated interviews, or (3) with repeated administrations via both modalities, patients learn to give similar information to both clinicians and the IVR system.

Poster No. 41

HAM-D 10 as a Goal of Antidepressant Treatment Evaluation

Max Fink M.D.[1], Charles Kellner M.D.[2], Rebecca Knapp Ph.D.[2], Wenle Zhao M.S.[2], Hilary Bernstein LISW[2], Teresa Rummans M.D.[3], Mustafa Husain M.D.[4], Georgios Petrides M.D.[1], Mark Beale M.D.[2], Kevin O Connor M.D. [3], A. John Rush M.D.[4]

[1] Long Island Jewish Medical Center-Hillside Hospital

Psychiatry Research 75-59 263rd Street

Glen Oaks, NY 11004

[2] Medical University of South Carolina, Charleston, SC
[3] Mayo Clinic, Rochester, MN
[4] University of Texas Southwest Medical Center, Dallas, TX

In most antidepressant treatment trials, a 50% or 60% reduction in a standard rating scale score (HAM-D or MADRS) from a serious illness rating baseline after 4 to 6 weeks of treatment is considered an endpoint indicating treatment success. Such a reduction, for example, in the HAM-D from scores of 30-35 leaves patients with scores of 12-17, an incomplete response. Such evaluations lead to extended treatment trials and inflated estimates of treatment efficacy.

In ECT, reductions in HAM-D to final scores of 10 within 6 to 8 ECT (2 -3 weeks) is the accepted standard. In the CORE* Continuation ECT versus Pharmacotherapy Trial for prevention of relapse in unipolar depression, the mean baseline HAM-D for 137 patients who have completed an index course of ECT was 35.5, and the final mean HAM-D was 6.9. Approximately 84% (115/137) of these patients met strict response criteria of HAM-D 10 at two consecutive ratings and 60% reduction from baseline.

Among the patients who responded to the index course of ECT, the degree of improvement was approximately 52% after the first three treatments, 63% after the first six treatments, and 84% at the end of the acute ECT course. The number of ECT ranged from 3 to 17 treatments (mean=7.2). Approximately 14% (16/115) met strict response criteria after 4 or fewer treatments, 49% (56/115) after 6 treatments and 70% (80/115) after 8 treatments.

More stringent criteria for the assessment of antidepressant treatment response in unipolar depression are feasible and should be routinely sought. (*CORE, Consortium for Research in ECT)

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Poster No. 42

Identifying Sources of Outcome Variability in Clinical Drug Trials.

Mary B. Hooper, B.A.[1], David J. Brunswick, Ph.D.[1], Jay D. Amsterdam, M.D.[1], and Charles Beasley, M.D.[2]

[1]Depression Research Unit, University of Pennsylvania Medical Center, 3600 Market Street – 8th floor, Philadelphia, PA 19104.

[2]Eli Lilly & Co., Lilly Corporate Center, Indianapolis, IN 46285.

The goal of a clinical trial is to differentiate the efficacy of an active drug from placebo using validated symptom-severity rating scales. The two most widely used scales for assessing efficacy in antidepressant drug trials are the Hamilton Depression (HAM-D) and the Clinical Global Impressions (CGI) severity scales. It is assumed that both scales are valid and will accurately reflect the severity of the depression with a consistently high correlation between scales. However, results from the FDA Summary Board of Approval (SBA) for 5 antidepressant drugs show inconsistent outcomes in studies using the HAM-D and CGI scales. In an effort to identify the sources of outcome variability in clinical trials, we examined inter-site variability in HAM-D and CGI ratings in a large, multi-site, prospective SSRI clinical trial.

Methods: Data were analysed from 839 patients who were treated prospectively with an SSRI for up to 10 weeks at five well-established university-based sites. All patients met DSM III-R criteria for major depression and had a baseline HAM-D_{17} score ≥ 16. Responders to treatment were defined by a HAM-D_{17} score ≤ 7. Evaluations of HAM-D_{17} and CGI severity ratings were made at each patient visit. All observations with a CGI score of 5 ("markedly depressed") were identified in the database and compared with the corresponding HAM-D_{17} score at the same visit. The site-specific concordance between these outcome scores was examined.

Results: The mean (± SD) and range for all HAM-D_{17} score observations with a corresponding CGI value of 5 was 24.1 ± 6.2 and 8 to 36, respectively, for all 5 sites combined. However, substantial differences between sites were observed for corresponding HAM-D_{17} scores at a CGI of 5:

	HAM-D_{17} Mean	HAM-D_{17} S.D.	HAM-D_{17} Range	N (%) HAM-D_{17} ≤ 21
Site 1	26.3 ± 3.0	3.0	19-36	7 (5%)
Site 2	27.1 ± 2.9	2.9	22-33	0 (0%)

Site 3	21.5 ± 4.2	4.2	8-35	100 (45%)
Site 4	25.7 ± 3.7	3.7	16-34	17 (15%)
Site 5	23.8 ± 3.7	3.7	16-35	39 (30%)

Conclusion: A high correlation between HAM-D_{17} and CGI outcome ratings is desirable in clinical trials. Both between- and within-site variability may affect the ability of a drug to differentiate from placebo.

Poster No. 43

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Poster No. 44

Acoustic Measures of Speech in Geriatric Depression Treated with Sertraline or Nortriptyline.

Murray Alpert, Ph.D.[1] Raul R. Silva, M.D.[2] and Enrique R. Pouget[1]

[1]Department of Psychiatry, HN 323, NYU Medical Center, 550 First Ave. NY, NY, 10016.
[2] St. Lukes/Roosevelt Hospital Center, 411 W. 144th St., N.Y., N.Y..

Paralinguistic measures of a depressed patient's speech can inform the clinician about various aspects of the patient's condition. Previous studies have examined automatic speech, such as counting or reading or free speech. We have explored the potential for adding acoustic measures of the patients' speech as an outcome measure in treatment trials since paralinguistic aspects of the patients' free speech can inform the clinician a
number of speech measures, involving both timing and prosody, have been reported as relevant for our purpose and we here report systemic study of measures that correlate with clinical ratings, measures that change with effective treatment, and the statistical power of acoustic measures in a clinical trial. Recordings were done at baseline and outcome in a trial comparing sertraline and nortriptyline in patients with geriatric depression. A group of age matched controls were also recorded in parallel with the treatment groups.

The sample consisted of 22 evaluable patients (12 males, 10 females), aged 60 to 79 years, (mean=67.4 yr.). All met DSM-III-R (1985) criteria for Major Depressive Disorder, without psychotic features. Patients were randomized to either sertraline, 50 to 150 mg/day (N=12) or nortriptyline, 50 to 100 mg/day (N=10) for up to 12 weeks following a 1 week placebo lead in. Efficacy was evaluated with the Ham-D and the BDI. The POMS is used to divide patients into retarded and agitated groups for the examination of speech timing. Recordings were done to coincide with the baseline and outcome ratings.

There was a highly significant reduction in Ham-D scores. The groups did not differ at baseline or outcome for Ham-D scores, but differed for BDI scores, suggesting differential subjective action. Productivity measures such as pausing and utterance duration, as well as measures of dyadic interaction, were related to depression severity measures at baseline and at outcome. The clinical ratings, on the whole, showed larger effect sizes but specific acoustic measures provide opportunities to examine individual behavioral sites of anti depressant drug action. The results are promising and it would be worthwhile to explore these relations in a larger sample. A battery of acoustic measures might provide a useful laboratory measure for the objective evaluation of clinically relevant behaviors.

Poster No. 45

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Poster No. 46

What Constitutes an "Adequate" Duration of Antidepressant Treatment?

David J. Brunswick, Ph.D.[1], Jay D. Amsterdam, M.D.[1], and Charles Beasley, M.D.[2]

[1]Depression Research Unit, University of Pennsylvania Medical Center, 3600 Market Street – 8th floor, Philadelphia, PA 19104.
[2]Eli Lilly & Co., Lilly Corporate Center, Indianapolis, IN 46285.

Background: The optimal length of treatment for most antidepressant drugs is not known. Although optimal duration for clinical efficacy is generally thought to be 6-8 weeks, some data have suggested that longer treatment periods may be needed to exploit an antidepressant's full therapeutic potential. As part of a large, prospective, multi-center study using a fixed dose of fluoxetine (20mg daily), we assessed the optimal duration of treatment necessary to achieve full remission of depressive symptoms.

Methods: A total of 169 outpatients (117 women, 52 men), with a mean (± SD) age of 39 ± 11 years were evaluated. All subjects met DSM-III-R criteria for major depression and had a baseline HAM-D_{17} score ≥ 16. All received fixed-dose fluoxetine (20mg daily) and were evaluated after 1, 2, 3, 4, 6, 8, and 10 weeks of treatment. 117 patients completed the 10 week trial and had complete HAM-D_{17} data for all of the treatment visits. Complete remission was defined as a HAM-D_{17} score ≤ 7, while responders had a HAM-D_{17} reduction ≥ 50% of baseline score.

Results: Mean HAM-D_{17} scores at each visit are shown along with the % of patients with HAM-D_{17} scores ≤ 7 and ≥ 50% of baseline values.

	HAM-D_{17} Mean ± S.D (n=117)	Number (%) of Pts with HAM-D_{17} ≤ 7	Number (%) of Pts with HAM-D_{17} decrease ≥ 50%
Baseline	22.2± 3.1	-	-
1 Week	20.0± 4.5	2 (2%)	4 (3%)
2 Weeks	17.8± 6.0	9 (8%)	18 (15%)
3 Weeks	15.4± 6.2	14 (12%)	30 (26%)
4 Weeks	13.5± 6.4	22 (19%)	42 (36%)
6 Weeks	10.9± 6.3	42 (36%)	63 (53%)

8 Weeks	9.0± 6.8	61 (52%)	77 (65%)
10 Weeks	6.6± 6.2	79 (68%)	98 (83%)

Repeated measures ANOVA followed by post-hoc Neuman Keuls or Duncan tests indicated that each HAM-D_{17} score was significantly lower than the score at preceeding visits ($p \leq 0.001$). The percentage of patients with a HAM-D_{17} score ≤ 7 continued to increase over time. Of the 51 patients with HAM-D_{17} score ≥ 16 at week four, 26 (51%) still became remitters at week 10 with a HAM-D_{17} score ≤ 7.

Conclusion: Response rates to fluoxetine 20 mg daily progressively and significantly increased during the time-period from week 4 to week 10. The number of responders, defined by a HAM-D_{17} score ≤ 7 more than tripled during this period. It appears that previous studies may have underestimated the overall effectiveness of antidepressant therapy due to the use of inadequate treatment durations.

Poster No. 47

Are There Sex Differences in Outcome With Antidepressants?

Frederic M. Quitkin, M.D., Jonathan W. Stewart , M..D., Patrick J. McGrath, M.D., Bonnie P. Taylor, M.A.

The New York State Psychiatric Institute
Columbia University Department of Psychiatry
1051 Riverside Drive, Unit #51
New York, New York 10032-2695

Few studies have examined the difference in outcome of men and women to antidepressants. There have been few notable exceptions. Specifically, the members of the Royal College, a British study, suggested that men had a superior response to imipramine compared to women (British Medical Research Council, 1965).

In a more recent examination of the predictive value of gender in determining outcome, Kornstein (1997) suggested that differences in pharmokinetics of men and women could contribute to differences on outcome of antidepressants. Specifically, women appear to have higher plasma levels of imipramine and amitriptyline with lower clearance of clomipramine. Steiner et al. (1993) reported that women had a superior response to paroxetine compared to men and a larger effect size compared to men.

Frank et al. (1988) characterized men s and women s responses as either normal responders who shared a rapid and sustained recovery by 8 weeks, or slow responders who took longer to become asymptomatic and a more varied course of recovery. They concluded that men were significantly more likely to show a rapid and sustained clinical response than women and indicated that percentages classified as normal responders differed by sex.

A concern in drawing conclusions from these studies is that they had modest sample sizes.

In order to examine whether gender was a significant predictor of antidepressant response we examined approximately 1200 men and women who took part in placebo vs. drug and drug vs. drug comparisons in the past 15 years in the Depression Evaluation Service, an outpatient research clinic. We examined the onset of proportion of persistent response by week for placebo, imipramine, phenlezine and prozac, and contrasted outcome by sex.

There was no consistent difference attributable to gender with any of these treatments. These data suggest that if severity, diagnosis, and chronicity are controlled for, there are no significant differences in outcome between the sexes with tricyclics, MAOIs, SSRIs and placebo. There was little evidence that either sex had a more rapid treatment response.

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Poster No. 48

Gender Differences In Mood During Tryptophan Depletion

Francisco Moreno MD *, Alan Gelenberg MD, Cindy McGahuey, and Pedro Delgado MD.

Department of Psychiatry, University of Arizona College of Medicine, 1501 N. Campbell Avenue, Tucson, AZ 85724

Although gender differences in the prevalence of depression have been extensively recognized, the effects of gender on symptom profile/severity, treatment response, and underlying mechanisms of illness and antidepressant action remain less clear. Plasma tryptophan (TRP) depletion is increasingly being used as a tool for determining the role of brain serotonin (5-HT) function in a variety of psychiatric disorders because of its simplicity, safety, and the robust behavioral effects observed in some patient groups. This study determines the differences in mood response to TRP depletion across genders.

Data were analyzed in 91 subjects (32 men and 59 women) who underwent TRP depletion at the Arizona Health Sciences Center. The sample analyzed included 16 healthy subjects, and 75 subjects with history of depression now in remission. Of the subjects with history of depression, 17 were medication-free, 18 were taking non-SSRI's, and 40 were taking SSRI's. Subjects had been administered a 102-gm, TRP-free, 15-amino acid drink. Ratings of mood were obtained at baseline, 5, and 7 hours after ingestion of the drink, and once during the following day. ANOVA with repeated measures was utilized to determine the main effect of time, and the interaction of time and gender.

For the group as a whole, TRP depletion caused a significant increase of HAM-D score ($F= 8.8$, $df= 3$, $p= .000$). Analysis of change in subgroups indicated that healthy subjects had no significant increase in HAM-D while subjects with history of depression had a significant increase in HAM-D. When data from all subjects is included, women had a larger increase in HAM-D score than men [mean(standard deviation) for men 6.31(4.37) vs. 11.33(8.60) for women ($p= .000$)]. However, when subjects are subgrouped, significant gender differences were seen only in those taking SSRI's at the time of testing. No gender differences were seen in the other subgroups. Preliminary analysis of individual HAM-D items in the sample as a whole suggests no differences in the pattern of mood response to TRP depletion across gender.

Although some studies have suggested greater (healthy) female susceptibility to the CNS biochemical (Nishizawa et al 1997) and behavioral effects of TRP depletion (Ellenbogen et al. 1996), we failed to find gender differences in the plasma TRP or depressive response to TRP depletion in healthy and non-SSRI treated subjects. It is possible that the limited sample size in some of the subject groups may account for the lack of statistically significant findings. These findings suggest that gender differences in depressive response to TRP depletion may be influenced by the type of antidepressant treatment being utilized at the time of testing.

Poster No. 49

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Poster No. 50

UTILIZATION AND COST COMPARISON OF INPATIENT ANTIDEPRESSANT DRUGS

Deborah L. Ackerman, M.S., Ph.D.[1], Alexander Bystritsky, M.D.[2]

[1]Department of Epidemiology, UCLA School of Public Health, Box 951772, Los Angeles, CA, 90095-1772
[2]Department of Psychiatry and Biobehavioral Sciences, UCLA Neuropsychiatric Institute and Hospital, Los Angeles, CA

Most studies in outpatient settings have found that the higher acquisition cost of the selective serotonin-reuptake inhibitors (SSRIs) may be offset by higher medical expenses associated with tricyclic antidepressants (TCADs). Little has been done to evaluate inpatient costs. This study was conducted (1) to provide descriptive information about inpatient antidepressant utilization and (2) to evaluate the relative costs associated with each drug class.

Inpatient antidepressant drugs were evaluated by a retrospective review of computerized billing and pharmacy data bases for all admissions between July 1, 1994 and July 1, 1997 to the UCLA Neuropsychiatric Hospital. Total charges for each class of drug were evaluated by analysis of variance, multiple regression, and by stratifying on diagnosis, severity, age, and other factors.

The SSRIs (primarily, fluoxetine, paroxetine, and sertraline) were prescribed to 46% of all patients; the atypicals (e.g., trazodone and bupropion) to 18%; the TCADS (most often nortriptyline, less often imipramine, amitriptyline, desipramine) to 8%; venlafaxine to 6%, and the monoamine oxidase inhibitors (e.g., phenelzine) to <1% of patients. Length of stay was a major factor in total charges for room, services, procedures, supplies, and tests. Generally older patients, especially those with more medical comorbidity, patients with severe affective disorder, patients who received more than one class of drug (22%), and patients who received only SSRIs or the atypicals also had the longest stays and highest total charges. The SSRIs were given to the youngest patients and were associated with low service and procedure charges. The atypicals were given to the oldest patients, most often non-mood disorder patients, and were associated with the highest service charges: $500-600 more than SSRIs, $600-$1000 more than venlafaxine, and $800 more than TCADs. The most important cost-component for the atypicals, after room charges, was ECT.

The atypicals and the SSRIs had the highest total charges. The atypicals were associated with the highest charges for services and procedures because they were prescribed more often to people who received ECT. Those patients may have been previous treatment failures. Conversely, relatively fewer ECT was performed on patients receiving the SSRIs. Better data are needed to determine whether utilization patterns are related to severity, prior treatment, or to physician preferences.

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Poster No. 51

SSRIs effects on vigilance and cognition

Jeroen Schmitt, MSc.[1], and Wim Riedel, Ph.D.[2]

[1]Experimental Psychopharmacology Unit, Brain & Behaviour Institute (UNS50), Maastricht University, P.O.Box 616, 6200 MD Maastricht, The Netherlands

[2] Experimental Psychopharmacology Unit, Brain & Behaviour Institute (UNS50), Maastricht University, P.O.Box 616, 6200 MD Maastricht, The Netherlands

Background: Arousal functions of the central nervous system involve among others widespread inhibitory serotonergic projections. Previous experiments have shown that subchronic administration of the SSRIs fluoxetine and venlafaxine, drugs otherwise devoid of cognitive impairment, leads to impaired vigilance performance in healthy volunteers.

Rationale: The current study was designed to compare the effects on vigilance and cognition of sertraline, an antidepressant acting by selective serotonin and dopamine reuptake inhibition, with the SSRI paroxetine and placebo.

Design: Healthy, non-depressed volunteers, aged 30-50, were studied in a double-blind, cross-over design. Sertraline in incremental (50-100 mg once a day) doses, paroxetine in incremental (20-40 mg once a day) doses, and placebo (in doses of one and two pills) - with a 14 day placebo washout between each of three 14 day testing periods - were administered. Doses were increased at day 7 after testing. Assessments, which included a 45-minute vigilance test (Mackworth Clock) and a battery of cognitive tests (immediate and delayed memory recall and recognition, short-term memory scanning, semantic memory retrieval, dichotic listening and stroop interference), occurred at pre-treatment baseline and on days 7 and 14 for each drug. Plasma concentrations of sertraline and paroxetine were measured on test days to confirm compliance.

Results: 24 subjects were included; 21 completed the study. Sertraline had no significant effect on vigilance performance, but paroxetine significantly impaired vigilance performance on days 7 and 14. Both drugs significantly impaired subjective sleep quality on days 7 and 14. Paroxetine (but not sertraline) significantly impaired delayed recall memory on days 7 and 14. Sertraline significantly improved strategy-driven retrieval from semantic memory as measured with the fluency test.

Comment: Paroxetine’s selectively impairing effect on vigilance is shared by other "serotonergic" anxiolytics and antidepressants, suggesting that interference with 5-HT transmission reduces arousal in particularly monotonous tasks or environments, or alternatively reduces arousal by decreasing subjective sleep quality. Pharmacological differences between the serotonergic reuptake inhibitors sertraline and paroxetine that may explain the observed results could lie in sertraline’s relatively higher dopamine reuptake inhibition property and paroxetine’s

relatively higher anticholinergic property. The former could attenuate the vigilance decrement which can apparently be attributed to serotonergic reuptake inhibition, whereas the latter might explain impaired delayed recall memory.

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Poster No. 52

Effects of Nortriptyline on Verbal Acquisition in Outpatients with Major Depression

Nunzio Pomara[1], M.D., Steve Choi[1], M.A., Binbin Shao[1], Ph.D. and Thomas B. Cooper[1], M.A.

[1] The Nathan S. Kline Institute for Psychiatric Research, 140 Old Orangeburg Rd., Orangeburg, New York 10962

Introduction: Recall across trials of a list-learning task such as the Buschke Selective Reminding Task (BSRT) is known to increase with repeated presentations of the same word list. Aging has also been found to slow down the rate of verbal acquisition. Several reports suggest that nortriptyline (NT) and other TCAs with marked central anticholinergic effects can adversely affect verbal memory. However, questions remain with regard to the effects of NT on the rate of verbal acquisition, as previous reports contained a small number of subjects, a restricted age range, few testing sessions, and usually no mention of the time of last dose. This report presents data on the effects of NT on the rate of acquisition in a broad age range of individuals with major depression, who were tested following acute challenges and during chronic treatment. The relationship of age as well as depression severity and NT-induced acquisition deficits was also examined.

Methods: Seventy-eight patients (ages 21-80, mean=50) who met the RDC and DSM-III criteria for major depression voluntarily agreed to participate in a six week double-blind trial whereby they received either NT or placebo following a one week single-blind placebo run-in. Individuals' drug dosages were adjusted weekly in accordance with the results of plasma NT levels, to maintain plasma drug levels within the therapeutic range. A comprehensive test battery that included the BSRT and Hamilton Depression Rating Scale (HDRS) was administered weekly before the morning dose. Each subject was also challenged with an acute dose of either NT (50 mg) or placebo, depending on random drug assignment, on the first and last day of chronic treatment. Performance in these acute sessions was assessed at baseline, 1.5 and 4 hours post-drug. Plasma drug levels were determined prior to each assessment. The BSRT consisted of 8 recall trials (7 selective reminding and delayed recall) of a 16-word list. Repeated measures ANCOVAs were performed separately for the two acute sessions and the chronic phase on word recall per trial, with Trial (1-8) and Time of assessment (baseline, 1.5 hrs and 4 hrs for the acute sessions, and week 0-6 for the chronic phase) as within-subjects factors, Treatment (NT vs. placebo) as the between-subjects factor, and age as a covariate. For the initial challenge, baseline HDRS score was also included as a covariate. To replicate and extend previous findings, the effects of chronic NT treatment in the elderly (age $\geq$ 60) and the young (age $<$ 60) were examined on the last day of chronic treatment.

Results: A significant Treatment x Trial x Time of assessment interaction was found for the initial acute challenge but not during chronic treatment or at rechallenge. Further analyses of the three times of assessment at initial challenge showed a significant Treatment x Trial interaction only at 4 hrs post-drug, indicating that NT group had a reduced rate of verbal acquisition. This interaction effect coincided with peak plasma drug levels and was not

significantly affected by age or depression severity. The significant interaction at initial challenge but not at rechallenge was consistent with tolerance development to this adverse effect of the acute NT dose. At the 6th week of treatment, we found a significant Treatment x Trial interaction in the elderly but not in younger subjects, suggesting that the rate of verbal acquisition in the early trials was reduced in the NT-treated elderly relative to placebo.

Conclusions: The initial acute NT (50 mg) challenge decreased the rate of verbal acquisition, and this effect was not influenced by age or depression severity. Tolerance to the adverse effect of the acute dose seems to develop following chronic treatment. Our data also suggests that chronic treatment with NT may slow the acquisition of verbal information in the elderly but not in the young.

(This work was funded by NIMH grant-MH44194.)

Poster No. 53

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Poster No. 54

COMPARING FLUOXETINE'S EFFICACY IN IMPROVING MOOD, PHYSICAL, AND SOCIAL SYMPTOMS ASSOCIATED WITH PMDD ACROSS THREE RANDOMIZED, PLACEBO-CONTROLLED IMPAIRMENT CLINICAL TRIALS

Eileen Brown, PhD (1), Steven J. Romano, MD (1), Teri Pearlstein, MD (2), and Meir Steiner, MD, PhD (3)

Lilly Research Laboratories, Lilly Corporate Center, DC 2423, Indianapolis, Indiana 46285

1. Brown University School of Medicine,Butler Hospital, 345 Blackstone Blvd. Providence, Rhode Island 02906

(3) St. Joseph's Hospital, Departments of Psychiatry and Biomedical Sciences,501 Charleton Ave. East, Hamilton, Ontario, Canada L8N4A6

Objective: A number of controlled trials have established fluoxetine's efficacy in treating PMDD. To evaluate fluoxetine's efficacy across three clinical trials differing in design and outcome measures, effect size (a unit-less measure of the difference in treatment means divided by estimated standard deviation) was calculated. Effect sizes of 0.5 and 0.8 are considered medium and large, respectively (Cohen, 1988).

Methods: Two studies used parallel designs comparing fluoxetine with placebo (one included a bupropion group). The third used a crossover design where patients received both fluoxetine and placebo. Diagnostic scales captured the salient mood, physical, and social impairment symptoms of PMDD. Primary outcome measure in the crossover study was average within-cycle change in score from follicular to luteal phase; the other two studies used change from mean baseline luteal phase scores to mean treatment luteal phase scores.

Results: Effect sizes for mood symptoms ranged from 0.6-1.2 across the three studies; for physical symptoms from 0.4-1.2 (two studies); and for social impairment 0.5-1.2. Effect sizes for total scores ranged from 0.5-1.4.

Conclusion: Medium to large effect sizes were seen with fluoxetine across three different clinical trials. Although different designs and outcome measures limit comparability across studies, calculated effect sizes support fluoxetine's efficacy in PMDD.

Poster No. 55

Characteristics of Placebo Baseline Responders in Aggressive Conduct Disorder.

Richard P. Malone, M.D.[1], Jacqueline R. Cater, Ph.D.[2], James F. Luebbert, M.D.[1], Mary Anne Delaney, M.D.[1] , and Roomana Sheikh, M.D.[1]

[1]MCP Hahnemann University; Eastern Pennsylvania Psychiatric Institute; 3200 Henry Ave.; Philadelphia, PA 19129.
[2]Biomedical Statistical Consulting, Wynnewood, PA.

Background: The most common reason for hospitalization of children and adolescents is to treat poorly controlled aggression. Several controlled trials of lithium in aggressive conduct disorder (CD) have reported that subjects display no or decreased aggression during placebo baseline (Campbell et al., 1984; 1995; Malone et al., 1994). The purpose of this study was to characterize placebo baseline responders (those not meeting the aggression criteria for randomization) who participated in a double-blind and placebo-controlled trial of lithium in aggressive CD. **Methods**: Subjects were 82 inpatients, 70 males and 12 females, ranging in age from 9.5 to 17.1 years (mean= 12.7 ± 2.00). All met DSM-III-R criteria for CD and were admitted with histories of chronic aggressive behavior. Study measures included the Conners Teacher Questionnaire (CTQ; Psychopharm. Bull., 1973), IOWA Conners (IOWA; Loney and Milich, 1982), Youth Self-Report (YSR; Achenbach, 1991), the Clinical Global Impressions (CGI; Psychopharm. Bull., 1985), Diagnostic Interview for Children and Adolescents (DICA; Reich et al., 1991), and Detrimental Psychosocial Factors Scale (Sanchez et al, 1994). In order to identify predictors of placebo baseline response, seven variables derived from these measures were entered into a series of univariate logistic regressions using the first baseline rating scores, and subsequently adding the change scores from the first to the second baseline rating. **Results**: Decreased severity of illness, aggressive type, and the presence of overanxious disorder were significant predictors of placebo baseline response, employing the first baseline rating. Decreased severity of illness and hyperactivity were significant predictors of placebo baseline response, employing the baseline change scores. **Significance**: Results suggest that more anxious children with lower severity of illness, hyperactivity, and aggression are more likely to be placebo baseline responders. These results will be compared to those reported by Campbell and associates (1995) and Sanchez and associates (1994), and their significance discussed.

This work was supported in part by NIMH Child and Adolescent Mental Health Award K07 MH00979 (Malone).

Poster No. 56

Psychometric Properties of the Social Phobia Inventory (SPIN): A New Self-Rating Scale

Kathryn M. Connor, M.D.[1], Jonathan R.T. Davidson, M.D.[1], L. Erik Churchill, M.S.[1], Nicholas L.A. Potts, M.D.[2], Andrew Sherwood, Ph.D.1, Edna Foa, Ph.D.[3], and Richard H. Weisler, M.D.[1,4]

Department of Psychiatry and Behavioral Sciences, Box 3812 Duke University Medical Center, Durham, North Carolina 27710

1. University of Adelaide, Adelaide, South Australia
2. University of Pennsylvania, Philadelphia, Pennsylvania
3. Private Practice, Raleigh, North Carolina

Background: Of available self-rated social phobia scales, none assesses the spectrum of fear, avoidance, and physiological symptoms, all of which are clinically important. Recognizing this limitation, the Social Phobia Inventory (SPIN) was developed.

Methods: Subjects were drawn from 6 different populations: 3 clinical trial samples; 2 control samples; and a random community sample participating in a telephone survey of mental health issues. Subjects were given the SPIN, a 17-item self-rated assessment measuring social phobia symptoms on a 5-point scale. Other scales in the validity assessment included the Liebowitz Social Anxiety Scale, Brief Social Phobia Scale, and Sheehan Disability Scale. IN the treatment samples, the Clinical Global Impressions Scales of Severity and Improvement were also rated.

Results: Good test re-test reliability, internal consistency, convergent and divergent validity were obtained. The SPIN distinguished between subjects and controls and demonstrated responsiveness to symptom change over time, reflecting different responses to active drugs vs placebo. Factorial composition identified 5 factors.

Conclusions: The SPIN demonstrates solid psychometric properties and shows promise as a measurement for screening of and treatment response to social phobia.

Acknowledgments are due to Atul Pande, M.D. and Brinda Wiita, M.D.

Supported in part by Social Phobia Grant 1R10-MH49339 to Dr. Davidson and by a grant from SmithKline Beecham

Poster No. 57

Pramipexole in the Treatment of Markedly Depressed Outpatients. Peter D. Londborg, M.D., Vincent Glaudin, Ph.D., and John R. Painter, Ph.D. Summit Research Network, 901 Boren Ave., Suite 1800, Seattle WA 98104

Introduction: Pramipexole, a full agonist for the dopamine D2 receptor, has been studied primarily in the treatment of Parkinson's disease and restless leg syndrome. **Purpose**: To evaluate the efficacy, tolerability and dosage of pramipexole in the treatment of major depression. **Design**: Double-blind, placebo-controlled, parallel groups randomized to one of 3 fixed doses of pramipexole (1mg, 3mg, or 7mg) or placebo for 8 weeks, with a post-study taper of 2 weeks. **Dosing**: Pramipexole 0.25mg twice a day was titrated to the fixed dose level over a period of up to 2 weeks. Dose reduction of 0.5mg was permitted per intolerance for the 1mg group; reduction of 1mg was permitted for the 3mg and 7mg patients. **Subjects**: Adult outpatients from Seattle (USA) who met DSMIII-R criteria for major depression were selected if total score on the Hamilton Rating Scale for Depression ($HRSD_{17}$) was at least 22 and depressed mood was rated at least 3 (item #1). **Measures**: Efficacy was assessed by mean change in $HRSD_{17}$ from baseline, by the Clinical Global Rating of Improvement (CGI-I) of at least much improved and by change in the Core Depression Cluster ($HRSD_{17}$ items 1,2,3 &7). Adverse events (AEs) were elicited at each visit, recorded in text, and converted to standard language. **Results**: *Efficacy*. 32 patients randomly assigned to each of 4 treatment conditions (n=9,8,8,&7 for placebo, 1mg, 3mg, and 7mg groups respectively) comprised the efficacy sample; 62% (20/32) completed 8 weeks of treatment. The 18 females and 14 males in the efficacy sample averaged 38 years of age; no significant differences among treatment groups for these demographic variables was found, nor were any significant differences observed in severity of depression at baseline. Mean $HRSD_{17}$ scores ranged from 23.1 to 25.1 and CGI-Severity from 4.75 to 5.25 at baseline. Repeated-measures ANOVA for $HRSD_{17}$ was significant for treatment group ($F=3.18$, $df=3$, $p<.039$) and approached significance for interaction between treatment and visit ($F=1.63$; $df=18$, $p<.057$). Pramipexole was significantly superior to placebo for the proportion of patients at least much improved at endpoint (Pearson $\chi^2 = 10.7$, $df=3$, $p<.013$); the greatest disparity was 75% (6/8) versus 0% (0/9) for 3mg and placebo respectively. Core depression (low mood and loss of interest) was significantly more improved for patients treated with pramipexole as assessed by repeated-measures ANOVA (main effect of group, $F=3.50$, $df=3$, $p<.028$; treatment by visit interaction $F=2.12$, $df=18$, $p<.007$). *Safety*. No serious AEs were recorded, but 48% (11/23) of patients were intolerant of pramipexole as the dose increased such that 71% (5/7) were intolerant of 7mg. Almost all patients (10/11) on active drug who dropped from treatment did so because of AEs, all associated with nausea. **Conclusions**: Pramipexole was demonstrated to be effective in the therapy of major depression of marked severity but its promise appears limited by intolerance (nausea). Further study is definitely warranted, especially in 2 and 3mg doses, because of its potential in treating severe and/or treatment-resistant depression. This potential is highlighted by impressive results in decreasing core symptoms of depression.

Poster No. 58

BUSPIRONE AND AMANTADINE TREATMENT OF SSRI ASSOCIATED SEXUAL DYSFUNCTION: A RANDOMIZED, PLACEBO CONTROLLED TRIAL

David Michelson, M.D, John Bancroft, M.D., Steven Targum, M.D., and Rosalinda Tepner, R.Ph.

Lilly Research Laboratories, Lily Corporate Center, DC 2423, Indianapolis, IN 46285

Objective: Few controlled trials of pharmacologic intervention in women with sexual dysfunction have been reported, and there is considerable uncertainty about both the usefulness of different agents and assessment methodologies. We evaluated the efficacy of buspirone and amantadine in the treatment of sexual dysfunction associated with fluoxetine administration.

Methods: This 12-week trial consisted of a 4-week baseline assessment period followed by an 8-week treatment period. Women who reported a deterioration in sexual function following initiation of fluoxetine therapy entered the assessment period and those who met entry criteria were then randomized to treatment with either buspirone, amantadine, or placebo. Outcomes were assessed using a patient-rated daily diary and a clinician-rated structured interview.

Results: All treatment groups (buspirone n=19, amantadine n=18, placebo n=20) improved significantly on overall, as well as most individual measures of sexual function, as assessed by both the patient diary and structured interview but there were no statistically significant differences among treatment groups. Compared with placebo, amantadine-treated women improved in mood and energy level, as assessed by the diary self-report.

Conclusion: Neither buspirone nor amantadine was more effective than placebo in ameliorating SSRI-associated sexual dysfunction. Most aspects of sexual dysfunction showed statistically significant nonspecific improvement, which was detected by both the patient-rated diary and the clinician-rated structured interview. Compared with placebo, amantadine was associated with further improvements in patient-reported mood and energy.

Poster No. 59

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Poster No. 60

Abstract Title: A Placebo-Controlled Study of Fluoxetine *vs.* Imipramine in the Acute Treatment of Atypical Depression

Patrick J. McGrath, M.D., Jonathan W. Stewart, M.D., Malvin N. Janal, Ph.D., Frederic M. Quitkin, M.D.

The New York State Psychiatric Institute
Columbia University Department of Psychiatry
1051 Riverside Drive, Unit #51
New York, New York 10032-2695

Background: The atypical subtype of depression appears to be both well-validated and common. While monoamine oxidase inhibitors (MAOI s) are quite effective in atypical depression, their side effects make them unattractive as a first treatment. The objective of this study was to estimate the efficacy of the selective serotonin reuptake inhibitor fluoxetine in the treatment of Major Depression with atypical features.

Method: One hundred fifty-four subjects with DSM-IV Major Depression who met Columbia criteria for atypical depression were randomized to fluoxetine, impramine, or placebo treatment for a 10 week clinical trial. Imipramine was included as an active comparison treatment because it is of known efficacy and more acceptable to patients than MAOI s.

Results: In both intention-to-treat and completer samples, both medications were significantly better than placebo and did not differ from one another. Significantly more patients dropped out from treatment with impramine than with fluoxetine. Prior to treatment, patients rated themselves very impaired on the psychological dimensions of general health and moderately impaired on physical dimensions, compared to population norms. Responders to treatment largely normalized on these measures.

Conclusions: Despite earlier data that SSRI s might be the treatment of choice for atypical depression, fluoxetine appeared to be no better than imipramine in this group, although it was better tolerated. Although fluoxetine may be less effective than monoamine oxidase inhibitors, its tolerability and superiority to placebo make it a reasonable first choice in atypical depression.

Poster No. 61

Venlafaxine in the Treatment of Dysthymia: An Open-Label Study

David J. Hellerstein, MD[1], Sarai Batchelder, PhD[1], Suzanne A.S. Little, PhD[1], Michael Fedak, MD[1], David Kreditor, MD[1]

[1]Department of Psychiatry, rm 2B34, Beth Israel Medical Center, First avenue at 16th St., New York, NY 10003

Background: Numerous studies have demonstrated the effectiveness of antidepressant medications in the treatment of dysthymia, or chronic depression. Venlafaxine blocks reuptake of both serotonin and norepinephrine, and may produce a more complete antidepressant response than single-mechanism SRIs. The purpose of this open-label study was to provide preliminary data on the tolerability and effectiveness of venlafaxine for patients with dysthymia. **Method:** Twenty-two dysthymic subjects were enrolled in this ten-week, open-label trial, and five dropped out prior to their 2nd visit. Seventeen (77.3%) subjects received more than one week of medication. **Results:** Of these 17 subjects, 13 (76.5%) (or 59.1% of the ITT sample) were treatment responders. Paired sample t-tests were highly significant, indicating that on average, there was significant improvement on all measures of symptomatology and functioning, with M$\pm$SD scores on the HamD decreasing from 20.87$\pm$6.36 at baseline to 6.06$\pm$5.49 at Week 10. The average dose at the time of response was 141.35 mg/day (sd=40.95). Side effects were reported by 17 (85%) subjects (the most common were fatigue, dry mouth, and nausea), and five patients (22.7%) discontinued treatment due to side effects, primarily nausea (n=3). **Conclusion:** These findings suggest the benefit of venlafaxine in the treatment of chronic depression, and the need for more rigorous studies.

This study was supported by a research grant from Wyeth-Ayerst Laboratories.

Dunner DL, Hendrickson HE, Bea C, Budech CB. Venlafaxine in dysthymic disorder. J Clin Psychiatry 1997; 58:528-531

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Poster No. 62

Deaths With Selective Serotonin Reuptake Inhibitor Treatment

Benjamin Roy, M.D., Sumner Goodman, M.D., Joseph Sacco, M.D., Reginald Peniston, M.D.

Stratton Albany VA Medical Center, 113 Holland Avenue, Albany, New York 12208

Because of their low potential for arrhythmias selective serotonin reuptake inhibitors (SSRIs) are deemed safe. However, no study controlled for the confounding effect of high protein binding of antidepressants to serum low density lipoproteins (LDL). Reduced LDLs increase while elevated LDLs obliterate free antidepressant. We collected mortality data retrospectively on 1000 unique patients examined between 1996 and 1998. Time of exposure to SSRI, dates of initiation of SSRIs, dates SSRIs were discontinued, and drug doses as well as, dates and values for serum cholesterol (91.7%) or LDL (33.9%) were determined by chart review and correlation with computer records. Patients were compared across different SSRIs with regard to serum cholesterol by a standardized ratio: [individual SSRI dose/ mean SSRI dose]/[individual serum cholesterol/mean serum cholesterol]. The mean ratio was calculated and three groups constituted: SSRI-naive patients, SSRI-treated patients <= 2SD, and SSRI-treated patients > 2SD. Deaths among SSRI-treated patients > 2SD [4/17 (23.5%)] was significantly higher than either SSRI-naive patients [14/531 (2.64%)] or SSRI-treated patients <= 2SD [7/378 (1.85%)]. Kaplan-Meier analysis of a computer randomized sample of 750 subjects was significant (Log rank = 18.00, df= 2, p< .0001). Cox regression analyses and Odds Ratio = 9.10, 95% Confidence Interval = 3.16-26.18 . Time of exposure to SSRIs was a mean 738 days, OR = 1.0, 95%CI = .9999-1.008. Two SSRI-treated patients > 2SD were on high dose SSRIs and had cholesterol > 290 mg/dl; while the remaining 2 patients were on ordinary doses with cholesterol < 100 mg/dl. Two patients complained of chest pain before their death while 2 died suddenly.

SSRIs and serotonin (5-HT) inhibit endothelial production of nitric oxide. Loss of endothelial-dependent vasodilation precipitates vasoconstriction to 5-HT and reduces coronary blood flow. SSRI-treated patients with LDL <= 110 mg/dl had a significantly higher incidence of chest pain than SSRI-naive patients (12/54 vs. 4/51; OR = 6.31; 95%CI = 1.58-25.21) with age as a cofactor (OR = 1.08; 95%CI = 1.02-1.15), and a paradoxically higher risk for chest pain than 10/110 SSRI-treated patients with hyperlipoproteinemia (OR = 3.27; 95%CI = 1.26-8.44).

Observational data has inherent biases. However, increased free SSRI due to reduced protein-binding to LDL or high doses that exceed protein-binding capacity may cause 5HT-induced microvascular spasm producing a syndrome of chest pain that is indistinguishable from angina pectoris due to coronary artery disease. The potential association with death requires confirmation by independent prospective investigation.

Poster No. 63

Superior Acute ECT Response in Psychotic versus Nonpsychotic Unipolar Depressed Patients

Charles Kellner M.D.[1], Rebecca Knapp Ph.D.[1], Hilary Bernstein LISW[1], Teresa Rummans M.D.[2], Mustafa Husain M.D.[3], Georgios Petrides M.D.[4], Mark Beale M.D.[1], Kevin O Connor M.D.[2], Wenle Zhao M.S.[1], A. John Rush M.D.[3], Max Fink M.D.[4]

[1] Medical University of South Carolina Institute of Psychiatry
67 President Street, P.O. Box 250861 Charleston, SC 29425
[2] Mayo Clinic Rochester, MN
[3] University of Texas Southwest Medical Center Dallas, TX
[4] Long Island Jewish Medical Center-Hillside Hospital Glen Oaks, NY

137 patients (35.5% psychotic) have completed an index course of bilateral ECT in the CORE* Continuation ECT vs Pharmacotherapy Trial. This is a multicenter, randomized study designed to compare the relative efficacy of continuation ECT vs continuation pharmacotherapy (lithium plus nortriptyline) for relapse prevention in patients with unipolar major depression. HAM-D (24-item) ratings were obtained three times per week. Approximately 84% of patients met strict responder criteria (HAM-D 10 at 2 consecutive visits and 60% reduction from baseline). Psychotic patients were more severely ill at baseline (mean HAM-D=38.1, versus 34.1 for nonpsychotic, p=0.037), and had a greater decrease ( ) in HAM -D scores from baseline to endpoint than nonpsychotic patients (mean se: psychotic, 32.0 2.2, nonspychotic 26.8 1.2; p=0.026). The average overall course length for those who completed the acute phase was 7.6 treatments with no overall difference between psychotic (mean=7.3) and nonpsychotic (mean=7.8) patients. However, among those who responded to ECT , approximately 19.5% (8/41) of psychotic patients required 4 or fewer ECT as compared to 10.8% (8/74) of nonpsychotic patients. Psychosis, a marker of illness severity, is associated with a particularly robust, and in some cases rapid response to ECT. (*CORE, Consortium for Research in ECT)

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Poster No. 64

Abstract Title: A Clinical Monitoring Format for Mood Disorders

Constance Guille, B.A., Amy Shriver, B.A., Christina Demopulos, M.D. and Gary Sachs, M.D.
Presenting author's primary affiliation:
Massachusetts General Hospital, WACC 812, 15 Parkman St., Boston, MA 02114
Additional author's primary affiliation:
Massachusetts General Hospital, Boston, MA

Objective: High quality systematic ratings can enhance the management of mood disorders, but standard formal rating scales are difficult to integrate into clinical practice. The Clinical Monitoring Form for Mood Disorders (CMF-M) was developed for routine clinical use. The present report evaluates the CMF-M dimensional sub-scales.

Method: Data was harvested from seven double blind clinical trials which utilized the CMF-M as well as the Hamilton Rating Scale for Depression (HRSD), the Young Mania Rating Scale (YMRS), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Mania Rating Scale (MRS) from the SAD-C. 500 follow-up visits in trials that enrolled bipolar patients (n=58) were included.

The CMF-M uses an alternative scoring method to rate severity of items in the Structured Clinical Interview for Diagnosis (SCID) current mood modules. Summing the items yields separate severity scores for depression (SUM-D) and mood elevation (SUM-ME). Based on severity ratings, SUM-D and SUM-ME scores, clinicians assign a Clinical Global Impression score (CGI), and a clinical status, (i.e., depressed, manic, hypomanic, mixed/rapid cycling, recovering, recovered, and/or roughening of symptoms), which correlate with standard rating scales and Diagnostic Statistical Manual IV (DSM IV) mood episode criteria.

Results: SUM-D highly correlates with the HRSD and the MADRS (r=0.79, r=0.87, respectively). SUM-ME highly correlates with the YMRS and the MRS (r=0.84, r=0.84), respectively.

Conclusion: SUM-D and SUM-ME are highly correlated with formal depression and mania rating scales. In routine clinical use the CMF-M can provide high quality dimensional data.

Poster No. 65

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Poster No. 66

DIVALPROEX vs. LITHIUM IN THE TREATMENT OF BIPOLAR DISORDER: A Naturalistic 1.7 year Comparison

S. Nassir Ghaemi, M.D.[1], Gary S. Sachs, M. D. [1], and Frederick K. Goodwin M.D.[2]

[1]Harvard Bipolar Research Program, Department of Psychiatry, Massachusetts General Hospital, 15 Parkman St., WAC-812, Boston, MA 02114

[2]Center on Neuroscience, Medical Progress, and Society, Department of Psychiatry, The George Washington University, Washington, D. C.

Objective: To provide naturalistic evidence of the comparative efficacy and tolerability of divalproex versus lithium in a real-world clinical practice setting.

Methods: All patients receiving lithium or divalproex in one year in a university outpatient psychiatry clinic were identified (n=43). Demographic and clinical variables were collected by chart review. Treatment response was based on standardized prospective rating scales (Clinical Global Impression, Global Assessment of Functioning, Hamilton Depression Rating Scale, and the Young Mania Rating Scale), supplemented by the retrospective Clinical Global Impression for Bipolar Disorder (CGI-BP). Mean duration of treatment with lithium or divalproex, which included prospective and retrospective periods, was 90 weeks.

Results: Lithium and divalproex were equally effective and tolerated, with statistically significant improvement in manic and depressive symptoms on all scales except the YMRS. Lithium non-responders responded well to divalproex (50%, 5/10), and lithium response in divalproex non-responders was similar (44%, 4/9), using the CGI-BP. Divalproex monotherapy was effective in treating depressive symptoms, with a 70% (7/10) response on the CGI-BP, and statistically significant improvement in the HDRS and CGI scales.

Conclusions: Lithium and divalproex were equally effective and tolerated in this naturalistic sample, but responders may represent distinct subgroups. Divalproex appeared effective in treating bipolar depression.

Sources of funding: Abbott Laboratories

Poster No. 67

Valproate vs. Lithium Pharmacotherapy in Bipolar Disorder Patients in Clinical Practice: A Retrospective Study

Robert Litman M.D.[1], Nina Gallauresi B.S.[1], Cynthia Gauss, M.D.[2], David Goldstein M.D.[2], Marc Hertzman, M.D.[1]

[1]Centers for Behavioral Health, 14915 Broschart Road, Suite 250,Rockville, MD 20850
[2] Department of Psychiatry, Georgetown University Medical School, Washington, DC

Although lithium carbonate is a proven effective treatment for bipolar disorder, it carries inherent risks to several organ systems as well as a significant side effects. The establishment of valproic acid as an effective treatment for bipolar disorder (Bowden et al, 1994) provides an alternative to the risks posed by lithium treatment. We assessed the indications and frequency with which patients with bipolar disorder on lithium therapy were switched from lithium to valproate therapy by reviewing the care of 108 stable patients treated with lithium and/or valproate in a university-based affective disorders clinic and an large affiliated private psychopharmacology practice from 1995 to 1998. Of 108 bipolar patients,45% were treated with valproate alone, 31% with lithium alone, and 8% (9 patients) were switched from lithium therapy to valproate therapy. Reasons for switching to valproate treatment from lithium included insufficient treatment response to lithium, sedation, and dermatological effects. CGI-S scores before and after the switch to valproate were minimally, moderately, or much improved in 8 of the 9 patients. Valproate treatment was well tolerated without side effects, except sedation in two patients. Data regarding the manner in which patients were switched to valproate therapy and time to treatment response on valproate will be discussed.

Poster No. 68

A Comparison of Brain Lithium Levels on Lithobid Versus Immediate Release Lithium

Michael E. Henry, M.D.[1], Constance M. Moore Ph.D.[2], Perry F. Renshaw, M.D., Ph.D. 3, Janis Breeze, S.B.[4], Eve P. Stoddard, B.A. [5], Christina M. Demopulos, M.D.[6], Gary S. Sachs, M.D.[7]

[1] McLean Hospital, 115 Mill Street, Belmont, Massachusetts 02148

[2]McLean Hospital, Belmont, MA, [3] McLean Hospital, Belmont, MA , [4] McLean Hospital, Belmont, MA, [5]McLean Hospital, Belmont, MA, [6] Massachusetts General Hospital, Boston, MA, [7] Massachusetts General Hospital, Boston, MA

Objective: To compare the brain lithium kinetics of Lithobid, a sustained release preparation of lithium, to the kinetics of immediate release preparations.

Background: Sustained release preparations of lithium are associated with lower peak serum levels but a greater area under the time concentration curve (AUC). We hypothesized that this would result in higher brain concentrations of lithium on the sustained release preparation than on the immediate release preparation.

Methods: 15 bipolar patients on a stable regimen of medications, including lithium, will be recruited from the outpatient clinics and via advertisement. Subjects are continued on their current regimen of lithium (either sustained release or immediate release medication) for one week. Subjects then undergo a magnetic resonance spectroscopy scan to measure brain lithium levels. Serum lithium levels are obtained immediately following the scan. Subjects are then converted over to the alternate lithium preparation medication at the same number of mg/day, and maintained on this preparation of lithium for at least two weeks. Spectroscopy scans and blood are obtained for the second preparation of lithium.

Results: 7/15 patients have completed at least one part of the study and it is anticipated that 15/15 will have completed by the end of March, 1999.

Discussion: Differences between serum and brain kinetics of the immediate and sustained release preparations and their potential clinical implications will be discussed.

Funded by Solvay Pharmaceuticals

Poster No. 69

Effectiveness of Traditional Antidepressants is Suboptimal in the Depressed Phase of Bipolar Disorder

Alan G. Mallinger, M.D.[1,2], Ellen Frank, Ph.D.[1], Michelle M. Barwell, M.D.[1], Michael E. Thase, M.D.[1] and David J. Kupfer, M.D.[1]

Departments of Psychiatry[1] and Pharmacology[2], University of Pittsburgh School of Medicine, WPIC, 3811 O Hara Street, Pittsburgh, PA 15213

Clinical testing of antidepressants is usually carried out with unipolar depressed patients. This reflects the fact that unipolar disorder is more prevalent, as well as the greater difficulty of conducting trials with bipolar subjects, given that antidepressants can induce manic episodes or mood cycling in such patients. There has been surprisingly little research to date on the specific effectiveness of antidepressant agents in bipolar disorder; indeed, it is often assumed that traditional antidepressants are comparably effective for treating virtually all types of depressive disorders, despite the limited existing evidence in support of this view. To begin to address this issue, we retrospectively reviewed the treatment records and mood ratings of patients who participated in one of two ongoing investigations (conducted in the same clinic) of maintenance treatment for bipolar or unipolar affective disorder, both of which required an index acute affective episode for inclusion.

DSM-IV diagnostic criteria were utilized. Bipolar patients were treated openly with tricyclic antidepressants (TCAs, mainly imipramine), monoamine oxidase inhibitors (MAOIs, mainly tranylcypromine), or selective serotonin reuptake inhibitors (SSRIs, mainly paroxetine). Unipolar patients had all failed an initial course of psychotherapy, and were subsequently treated openly with SSRIs (mainly fluoxetine). Mood ratings were routinely performed at all clinic visits by an independent evaluator. Clinical response was determined based on improvement over baseline scores on the Hamilton Depression scale.

There were 57 bipolar patients (53 bipolar I, and 4 schizoaffective, bipolar type). For the first trial with antidepressants, only 33% of those started on drug (intent to treat) responded to TCAs (6/18), 55% to MAOIs (12/22), 46% to SSRIs (6/13), and 50% to other drug types (2/4). There were no significant differences in response rates for the different classes of antidepressants; the overall response rate for bipolar depression was 46%. In contrast, the intent to treat response rate among 86 recurrent unipolar depressed subjects was 73%, and the difference in the proportionality of response between bipolar and unipolar patients was highly significant (chi square=9.999, $p<0.002$). Among the bipolar subjects, the percentage of patients who did not complete at least four weeks of treatment in the first trial was 6% for TCAs, 18% for MAOIs, and 15% for SSRIs. Bipolar subjects who did not respond in the first trial or who subsequently relapsed were treated with successive trials of different antidepressants. In all, 123 separate treatment trials were performed. Only 35 patients (61%) ultimately responded to one of the antidepressants administered during the study. Because we previously demonstrated the

superiority of tranylcypromine over imipramine for treating anergic bipolar depression, we also compared the first trial outcome for TCAs vs. MAOIs, including only those subjects who had at least four weeks of treatment. The response rates were 35% for TCAs (6/17) and 67% for MAOIs (12/18), a difference that was marginally significant (Fishers Exact Test (one tailed), p=0.06). There was no difference in response to MAOIs between patients categorized as anergic (n=12) or non-anergic (n=6) (67% in both groups).

These findings support the idea that traditional antidepressants are less effective in bipolar than in unipolar depression. Among the available agents, MAOIs may be a better choice than TCAs. The search for more effective treatments for bipolar depression should be a major priority.

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Poster No. 70

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Poster No. 71

Topiramate as add-on Adjunctive Treatment for Patients with Bipolar I or Schizoaffective - Bipolar Type Disorder experiencing either a Manic or Mixed Episode

K. N. Roy Chengappa, M.D., F.R.C.P.C.[1,2,3], Dilip Rathore, M.D.[2], Joseph Levine, M.D., M.A.Sc.[1,3],
Rebecca Atzert, R.N. [1,2,3], Lalith Solai, M.D.[1], Haranath Parepally, M.D.[1,2], Harry Levin, M.D.[1]
Nicholas Moffa, M.D.[1], Joyce Delaney, R.N.[1,2], Jaspreet S. Brar, M.D., M.P.H.[1]

Western Psychiatric Institute & Clinic, University of Pittsburgh Medical Center

1. Special Studies Center @ Mayview State Hospital, Bridgeville, PA
2. Stanley Center for the Innovative Treatment of Bipolar Disorder, Pittsburgh, PA

Presenting Author:

K. N. Roy Chengappa, M.D., F.R.C.P.C.
Associate Professor of Psychiatry
Western Psychiatric Institute & Clinic
Special Studies Center @ Mayview State Hospital
Stanley Center for the Innovative Treatment of Bipolar Disorder
3811 O'Hara Street
Pittsburgh, PA 15213-2593

Objective: Anticonvulsant agents- carbamazepine and valproate are alternatives to lithium in treating subjects with bipolar disorder. Topiramate (Topamax®), a new antiepileptic agent and candidate drug for bipolar disorder has an attractive advantage, weight loss. We evaluated topiramate as an adjunctive treatment for bipolar patients. **Methods:** Patients with DSM-IV Bipolar I disorder [n = 14, mania (n = 10), hypomania (n = 1), mixed episode (n = 3), rapid cycling (n = 5)], and Schizoaffective disorder-bipolar type (n = 2) resistant to current mood-stabilizer treatment were initiated on topiramate, 25 mg per day, increasing by 25 to 50 mg every 3 to 7 days to a target dose between 100 to 300 mg per day as other medications were held constant for 6 weeks. The Young-Mania, Hamilton–Depression, and CGI-bipolar version scales were used to rate subjects weekly. **Results:** By six weeks, nine (56%) subjects were responders, i.e. 50% reduction in the Y-MRS scores and a CGI of "much" or "very much improved". Two subjects were "minimally improved", four showed no change, and one was "minimally worse". Five subjects had parasthesia, three experienced fatigue and sedation, two had "word-finding" difficulties, one each had diarrhea, rash, and delirium, in all cases side effects were transient and resolved. All patients lost weight - mean of 10.3 lb. in 6 weeks, and a significant reduction in body mass index (BMI) occurred too. **Conclusions:** Topiramate has efficacy for the manic and mixed phases of bipolar illness. Other preliminary data suggests antidepressant efficacy too. It has the added advantage of weight loss. If controlled trials confirm these initial results, topiramate may be a significant addition to the available treatments for bipolar disorder.

Poster No. 72

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Poster No. 73

Long-Term Olanzapine Treatment: Efficacy and Safety in Manic Patients With and Without Psychotic Features

M. Tohen, MD, Dr.PH., T. Jacobs, MAS, K.S. Gannon, PhD., T.M. Sanger, PhD., M. Greaney, MS, V. Toma, BS, G. D. Tollefson, MD, PhD.

Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285

A 49-week, open-label olanzapine extension phase was conducted after a 3-week, double-blind study of olanzapine vs. placebo in bipolar I patients, manic or mixed episode. Patients (N=113, 82% manic; 46% without psychotic features) entered open-label extension and received 5-20 mg/day of olanzapine (average modal dose=13.8 mg/day) for an average of 201 days. The Y-MRS was used to assess mania. Cognitive function was assessed using the Positive and Negative Syndrome Scale (PANSS) Cognitive component. An additional PANSS factor, Hostility, was also used. Safety assessment of olanzapine included: EPS, including pseudo-parkinsonism (Simpson-Angus Scale), akathisia (Barnes Akathisia Rating Scale) and dyskinesias (AIMS); discontinuations due to adverse events; ECGs and depressive symptoms (HAMD-21).

Patients showed statistically significant improvement in manic symptoms. Mean change from baseline to endpoint was -18.01 on the Y-MRS (baseline=25.49, $p<.001$). There was no significant difference in antimanic response based on the presence or absence of psychotic features at the index episode ($p=.310$). Cognitive functioning (PANSS Cognitive component) showed significant improvement in a mean change from baseline to endpoint of -6.33 (baseline=17.66, $p<.001$). Also, a significant improvement on the PANSS Hostility factor was found (mean change=-4.50, baseline=10.65, $p<.001$).

There were improvements in mean change from baseline to endpoint on the Simpson-Angus (-0.42, $p=.043$) and Barnes Akathisia Scale (-0.13, $p=.080$); and no statistically significant worsening on the AIMS total (0.03, $p=.727$). No patient experienced tardive dyskinesia during the study. Seven (6.2%) patients discontinued therapy due to an adverse event. There was no significant mean change from baseline to endpoint in QT_C interval (0.10 msec, $p=.971$). Mean improvement from baseline to endpoint on the HAMD-21 was -5.77 (baseline=12.17, $p<.001$).

Results suggest that olanzapine is safe and effective in the long-term treatment of mania, with or without psychotic features, and appears to exert a beneficial effect on cognitive functioning as measured by the PANSS Cognitive component. Overall, olanzapine was well tolerated with very few extrapyramidal symptoms and no clinically significant changes in labs, vitals, or ECG parameters.

Poster No. 74

Changes in health-related quality of life of patients with bipolar disorder treated with olanzapine

M. Namjoshi, PhD., T. Jacobs, M.S.S., T.M. Sanger, PhD., K.S. Gannon, Ph.D., M. Tohen, MD, Dr.PH, A. Breier, MD

Eli Lilly and Company, Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN 46285

Introduction: The objective of the study was to determine the changes in health-related quality of life of patients with bipolar disorder when treated with a new atypical antipsychotic olanzapine. Methods: One hundred and thirty nine patients with a confirmed diagnosis of bipolar disorder were enrolled in a randomized, placebo-controlled clinical trial. The study design comprised a 3-week acute phase in which 70 patients were randomized to olanzapine and 69 patients to placebo. This was followed by an open-label extension phase in which all patients were treated with olanzapine. Health-related quality of life of the patients was assessed using the Medical Outcomes Study - Short Form 36 (SF-36) which covers eight quality of life dimensions. Quality of life was measured at baseline, at the end of the acute phase, and finally, at the end of the 49-week open-label extension phase. Results: The mean age of patients in the study was 40 (sd=10.9), with 52% of patients being male. In the acute phase, 65 patients on olanzapine completed the SF-36, while 57 patients on placebo provided quality of life data on the SF-36. Of the 113 patients that entered the open-label extension phase, 82 completed the SF-36. In the acute phase, statistically significant improvements were seen in the physical functioning dimension in patients treated with olanzapine compared to those treated with placebo ($p=.016$). In the open-label 49-week extension phase, statistically significant improvements over baseline were observed on the dimensions of bodily pain ($p<.001$), social functioning ($p=.004$), role-emotional ($p=.030$), and general health ($p=.009$). There was, however, a statistically significant decrease in the vitality score over the extension period ($p=.002$). The results of this study show that olanzapine positively and significantly impacts several dimensions of health-related quality of life in patients with bipolar disorder.

Poster No. 75

Olanzapine versus Haloperidol in Schizoaffective Disorder, Bipolar Type: Repeated Measures Analyses of Efficacy and Cognitive Function

Fan Zhang, PhD., Mauricio Tohen, MD, Dr.PH., Todd Sanger, PhD., Kimberley S Gannon, PhD., Gary D Tollefson, MD., Alan Breier, MD.

Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN 46285

In a sub-sample of a large multicenter, double-blind study comparing olanzapine against haloperidol, 177 patients with Schizoaffective Disorder, Bipolar Type, currently manic (N=28), currently mixed (N=47), currently depressed (N=53) and currently euthymic (N=49) were assessed at baseline and then weekly for 6 weeks. Six items of the BPRS (extracted from the PANSS) comprised the BPRS Mania total score (sum of the following items: conceptual disorganization, excitement, grandiosity, hostility, tension, disorientation). Cognitive functioning was measured with the PANSS Cognitive Component (sum of the following items: difficulty in abstract thinking, stereotyped thinking, cognitive disorganization, lack of judgment and insight, poor attention, tension, mannerisms and posturing). In addition, patients were assessed using the Montgomery-Asberg Depression Rating Scale (MADRS) at baseline and only at Week 6.

Significantly more patients in the olanzapine group (28.7%) than the haloperidol group (10.7%) had 40% or more improvement on the BPRS Mania total score (p=.011). On the PANSS Cognitive Component, significantly more patients in the olanzapine group (20.0%) than the haloperidol group (7.1%) had 40% or greater improvement (p=.043).

Repeated measures analyses of the Mania total and the Cognitive Component scores were performed on each subgroup of patients (manic, mixed, depressed, and euthymic). On the BPRS Mania score, currently manic patients randomized to olanzapine had an average reduction of 1.13 per week compared to a reduction of 0.53 for the haloperidol group (p=.075); currently depressed patients treated with olanzapine had an average reduction of 0.57 per week compared to an increase of 0.11 for the haloperidol-treated group (p=.028). On the PANSS Cognitive Component score, currently manic patients randomized to olanzapine had an average score reduction of 1.09 per week as compared to 0.22 for the haloperidol group (p=.050), and currently depressed patients randomized to olanzapine had an average reduction of 0.86 as compared to an increase of 0.37 for the haloperidol group (p=.002). Analysis of the MADRS score (mean change from baseline) indicated that currently depressed patients treated with olanzapine had an average reduction of 8.57 compared to an increase of 6.63 for the haloperidol-treated patients (p=.0001).

Relative to haloperidol, olanzapine produced a significantly greater improvement in manic symptoms (BPRS Mania total score) in currently depressed patients, a significantly greater improvement in cognitive functioning (PANSS Cognitive Component) in patients currently manic or depressed, and a significantly greater reduction of depressive symptoms (MADRS) in patients currently depressed. A numerically greater improvement was observed for each score in

all other subtypes. Overall, results indicate that olanzapine appears to have mood stabilizing properties in this patient population.

Poster No. 76

Clinical Studies Confirm Preclinical Selectivity of M100907 for the 5-HT2 Receptor

Steve J. Offord, Ph.D.[1] Norman Huebert, Ph.D.[1], Francoise Brunner, Ph.D.[2], and Steve Sorensen, Ph.D.[1]

[1]Hoechst Marion Roussel, PO Box 6800, Bridgewater, NJ 08807-0800

[2]Hoechst Marion Roussel, Romainville, France

M100907 has been shown to be a potent and highly selective 5-HT2A receptor antagonist in vitro, with a Ki of 0.6 nM for the cloned rat 5-HT2A receptor and Ki's of at least 100-fold higher for a variety of other receptors, including D2. The in vivo selectivity of M100907 was evaluated in rats using the protein alkylating agent N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) and in humans by positron emission tomography (PET) using the radiotracer [11C]NMSP. Plasma samples were obtained for correlation with receptor occupancy in all studies. Rats were pretreated with M100907; 6 rats were assigned to each of 6 dose groups: 0.01, 0.1, 0.3, 1, 3, and 10 mg/kg. One hour after M100907 administration, EEDQ (10 mg/kg) was injected intraperitoneally. The rats were sacrificed for analysis of 5-HT2A and D2 receptor levels. In 2 open-label PET studies, receptor occupancy, time course, and relationship to plasma concentrations of M100907 were assessed after a single oral dose of the drug in healthy volunteers. In one study, 6 subjects received 3 oral doses of M100907 with each dose administration separated by a 1-week washout period. Doses evaluated were 1, 2, 6, 9, 18, and 72 mg. In the second study, the time course of 5-HT2 receptor occupancy was evaluated in 9 volunteers who received either 10 or 20 mg of M100907. PET was conducted at baseline and at 3 consecutive time points after the dose, either 2, 5, and 8 hours or 2, 8, and 24 hours.

Pretreatment of rats with M100907 dose dependently protected the 5-HT2A receptor from alkylation by EEDQ with maximum protection at doses between 1 and 10 mg/kg (ED50 = 0.035 mg/kg). However, doses up to 10 mg/kg M100907 did not protect D2 receptors. The calculated affinity ratio is >286. Results of PET studies determined that 5-HT2 receptor occupancy ranged from 82% to 87% by kinetic analysis after each dose of 10 or 20 mg. Occupancy was maintained for 8-12 hours following a single oral dose of 10 or 20 mg. After 24 hours, receptor occupancy was maintained with the 20-mg dose but was decreased by 18-21% following the 10-mg dose. Binding of [11C]NMSP to receptors in the striatum (D2 receptors) was not displaced by M100907. These results confirm the selectivity of M100907 for the 5-HT2A receptor as determined in previous in vitro experiments. The plasma concentration correlating with the ED50 in rats was 0.67 ng/mL, while receptor saturation in the PET studies was observed at plasma concentrations of 1 ng/mL. It is reasonable to expect an increase by a factor of two in concentration could take the ED50 to an ED90 (ie, 0.67 x 2 =1.34 nM, a concentration very close to PET saturation). This comparison demonstrates a remarkable similarity between animal in vivo occupancy findings and those in man.

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Poster No. 78

Who Should Do Assessments in Treatment Trials? A Comparison of Clinician Versus Independent Assessors in a Multicenter Schizophrenia Treatment Study

Delbert Robinson, M.D. [1], Marjorie McMeniman, Ph.D.[1] and Margaret Woerner, Ph.D.[1]

[1]Hillside Hospital, Research Department, Glen Oaks, NY 11004 USA

Everyone who designs treatment trials must decide who will do assessments for the trial. The usual options are either the clinicians who treat the subjects in the trial or independent assessors who are not directly involved in the care of subjects. The use of independent assessors allows ratings to be done without knowledge of treatment condition while patients receive open-label treatment. This option is often more acceptable to patients, their families and clinical staff than the double-blind treatment required if clinicians are to make assessments without knowledge of treatment assignment. However, independent assessors typically have less contact with subjects than clinicians; clinicians also often receive collateral information from ancillary clinical staff which may not be available to independent assessors. The combination of infrequent contact and restricted information sources may limit the ability of independent assessors in comparison with clinician assessors to elicit symptoms from subjects; these factors may be especially important for studies with psychotic subjects who may not volunteer symptoms readily due to suspiciousness or lack of awareness of their symptoms.

Our opportunity to compare clinician and independent assessor ratings arose in the context of the National Institute of Mental Health Treatment Strategies in Schizophrenia Study (TSS). Three hundred thirteen subjects with schizophrenia or schizoaffective disorder at 5 centers were treated under double-blind conditions and assessed for 2 years. BPRS and CGI Severity of Illness assessments were done by treating psychiatrists (n = 10) and independent raters (n = 10) at baseline, after 28, 52, 80 and 104 weeks of double-blind treatment and during periods of symptom exacerbation. Data for the analyses consist of 1627 assessments which were completed by both a psychiatrist and an independent rater. Results comparing psychiatrist and independent assessor ratings on BPRS symptom factors and CGI scores will be presented at the meeting.

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Poster No. 79

Relationship between Mood Disturbance in Schizophrenia and Quality-of-Life

Scott W. Andersen, M.S., Gary D. Tollefson, M.D., Ph.D.

Eli Lilly and Company, Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN 46285

The main objective in the treatment of schizophrenia should be to optimize individual patient functioning and quality-of-life (QOL). To enhance an individual's chance to reintegrate, improvement across the widest spectrum of schizophrenic symptomatology—including non-traditional disease associated symptoms other than delusions and hallucinations—should be sought. One example is concurrent mood disturbance. Such a factor would be expected to adversely impact the patient's perception of QOL. QOL in schizophrenia may be adversely affected by a variety of factors including duration of illness, cumulative hospitalization days, tardive dyskinesia, and magnitude of negative symptoms. However, less is known about the possible relationship of concurrent mood symptoms. The hypothesis of these analyses was that the QOL for people with schizophrenia would be inversely related to the severity of concurrent mood disruption.

Post-hoc analysis was conducted of an international, multi-center, double-blind, 28-week study of 339 patients who met DSM-IV criteria for schizophrenia, schizophreniform, or schizoaffective disorder. QOL data were collected at baseline, 8, 16, 24, and 28 weeks or at early discontinuation; PANSS data were collected at each visit (weekly to week 8 and monthly thereafter). Correlations were calculated between changes in QOL (QLS Total and subscales) and PANSS Mood score. Regression models were used to determine the proportion of variability in the QLS total and subscores accounted for by changes in PANSS Positive, PANSS Negative, and PANSS Mood scores. Finally, a statistical path analysis was performed to determine the mechanisms used by the PANSS Mood scores to affect the QLS total and subscores. All analyses used an LOCF algorithm.

The correlations of PANSS Mood on the QLS total and subscores were statistically significant with the strongest correlation against the Interpersonal Relations (QLS_IPR) subscore. The path analysis results indicate that the PANSS Mood most significant path in affecting QLS total and QLS_IPR is direct as opposed to indirect through affecting PANSS positive and PANSS Negative scores which in turn affect QLS total and QLS_IPR.

Changes in QOL of schizophrenic patients is inversely related to changes in the concurrent mood disruption. Early therapeutic interventions directed at a broader constellation of schizophrenic symptomatology, including mood, may be helpful in improving a patient's QOL. With the introduction of novel antipsychotic agents earlier in the course of illness, their possible relative advantages in restoring individual QOL merit further investigation.

Poster No. 80

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Poster No. 81

Response of Chronic Nonresponding Schizophrenic Patients to Olanzapine: Clinical and Neurocognitive Effects .

Robert C. Smith M.D., Ph.D.[1], Mauricio Infante M.D.[2], Abhay K. Singh M.D.[2], Vasmi K. Garlapati M.D.[2], Akeela Ali BA[2]

[1] Department Psychiatry, NYU Medical School & Manhattan Psychiatric Center, C/O P.O. Box 316, Hewlett, N.Y., 11557
[2] Manhattan psychiatric Center, Wards Island, New York 10035

Olanzapine is an atypical neuroleptic, which has shown to have efficacy on positive and negative symptoms in schizophrenia. Although olanzapine's receptor binding profile is somewhat similar to clozapine, there are conflicting reports on its potential efficacy in the subgroup of schizophrenic who are medication refractory and hospitalized for many years in tietary care facilities. To assess the efficacy of olanzapine on clinical improvement and neurocognitive functioning in chronic nonresponding schizophrenics we conducted a double-blind study of olanzapine (20 mg/day) and haloperidol, with open label olanzapine follow-up of up to 40 mg/day. Clinical assessment was done with PANSS and SANS rating scales and CGI. Neurocognitive assessment used a series of tests measuring executive function and verbal and visual-spatial memory. Interim analysis of results on 32 patients showed that higher doses of olanzapine (30-40 mg/day) had a significant effect on reducing negative symptoms after several months of treatment in the open phase. There was a trend for greater improvement on olanzapine than haloperidol during the 8-week double-blind phase, but most differences were not statistically significant. Results of neurocigntive tests showed positive effects for olanzapine. Compared to haloperidol, olanzapine significantly improved performance on the Wisconsin Card sorting task (WCS) and accuracy on two-choice reaction time at the end of the double-blind compared to baseline testing. There were nonsignificant trends for more improvement on olanzapine than haloperidol on some other measures of verbal learning and memory at the end of the double-blind phase. At the end of the open olanzapine phase, performance on paired words (RANDT) and Sternberg memory task were improved over baseline. Olanzapine haloperidol improved visual-spatial memory at the end of the open olanzapine phase, but there were no differences between olanzapine and haloperidol after only 8 weeks of the double-blind treatment. Olanzapine's effects on improving neurocognitive performance were not strongly correlated with its effects on changes in rating scale clinical symptom scores. There were no significant changes in neurological soft signs produced by either olanzapine or haloperidol. The effects of olanzapine on performance on WCS, RANDT and Sternberg memory suggest that olanzapine may have ameliorative effects on neurocognitive functions involving verbal memory and executive functions. The lack of significant correlations between the effects of olanzapine on neurocognitive and clinical improvements suggest that these may be separate domains of clinical effects.

Poster No. 82

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Poster No. 83

Quetiapine and Risperidone in Outpatients with Psychotic Disorders: Results of the QUEST Trial

Jamie Mullen[1], M.D., Michael Reinstein[2], M.D., Mohammed Bari[3], M.D., Lawrence Ginsberg[4], M.D.,
and Nat Sandler[5], M.D.

[1] Zeneca Pharmaceuticals, 1800 Concord Pike, PO Box 15437, Wilmington, DE 19850-5437
[2] Forest Foundation, Chicago, IL
[3] Synergy Clinical Research Center, Chula Vista, CA
[4] Red Oak Psychiatry Associates PA, Houston, TX
[5] University of Kentucky, Lexington, KY

In a 4-month, multicenter, open-label trial, the tolerability and efficacy of quetiapine fumarate (quetiapine, SEROQUEL®) and risperidone were compared in 751 adult outpatients with psychotic disorders. Patients were randomized in a 3:1 ratio (quetiapine: risperidone) and were flexibly dosed. Assessments included the extrapyramidal symptoms (EPS) checklist, the Hamilton Rating Scale for Depression (HRSD), the Clinical Global Impression (CGI), the Positive and Negative Syndrome Scale (PANSS), and the Drug Attitude Inventory (DAI-10). At the completion of the trial the mean quetiapine dose was 253.9 mg and the mean risperidone dose was 4.4 mg. EPS events in both treatment groups declined over the 4-month treatment period, with no significant differences between groups in the overall occurrence of EPS. Patients in the risperidone group were more likely to have an EPS event and more likely ($p<0.001$) to have EPS that required adjustment of study medication or adjunctive medication than were patients in the quetiapine group. Excluding mild EPS symptoms, EPS symptoms rated as "at least moderate" occurred more frequently at each visit in risperidone patients. The quetiapine and risperidone groups had improvements in all efficacy measures. The quetiapine group had significantly ($p=0.0280$) greater improvement in HRSD than the risperidone group. A higher percentage of patients in the quetiapine group relative to the risperidone group had improvement in the CGI at each visit. No statistically significant differences between groups were evident in the PANSS positive scale, negative scale, general psychopathology score, or total score, nor was there a statistically significant difference between groups in the DAI-10. In summary, quetiapine was less likely than risperidone to require dose adjustment for EPS or concurrent anti-EPS medication, was more effective than risperidone in treating depressive symptoms, and was as effective as risperidone in treating the positive and negative symptoms of outpatients with psychosis.

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Poster No. 84

Switching from Risperidone to Ziprasidone: An Interim Analysis of a 6-week Study

George Simpson, M.D.,[1] Stephen Potkin, M.D.,[2] Peter Powchik, M.D.,[3] and the Switch Study Group

[1] LAC+USC Medical Center, Dept., of Psychiatry, Psychiatric Outpatient Clinic, Graduate Hall, 1937 Hospital Place, Los Angeles, CA 90033, USA
[2] University of California, Irvine, Orange, USA
[3] Pfizer Pharmaceuticals Group, New York, USA

The objective of this study was to investigate stable outpatients with schizophrenia, primarily seeking enhanced efficacy, who were switched from risperidone to ziprasidone.

This was an interim analysis of a 6-week, randomized, blinded-rater study in which stable outpatients (*n*=24) were switched from risperidone to ziprasidone 40–160 mg/day. Assessments included the PANSS, CGI, and a battery of cognitive tests, as well as standard safety and tolerability monitoring.

Statistically significant improvements were seen in the PANSS total score and the negative, positive, and cognitive subscales. The majority of patients (61%) were rated as improved on the CGI and only one discontinued due to inadequate efficacy. Also notable were the significant improvements in assessments of cognitive function, specifically: a computerized Continuous Performance Test, the Rey Verbal Learning Test, verbal fluency, Digit Span Distraction, and the Wisconsin Card Sorting Task. Ziprasidone was well tolerated. In addition, prolactin and triglyceride levels decreased substantially (85% and 13%, respectively).

The significant improvements in psychopathology and cognitive function in these patients switched from risperidone to ziprasidone are encouraging. Improvements in attention, vigilance, verbal learning and recall, and executive function indicated by these results, suggest that ziprasidone has a beneficial effect on cognitive function in patients with schizophrenia

Poster No. 85

Switching from Olanzapine to Ziprasidone: An Interim Analysis of a 6-week Study

David Daniel, M.D.,[1] Robert Stern, M.D.,[2] Thomas Kramer, M.D.,[3] Peter Powchik, M.D.,[4] and the Switch Study Group

[1] Clinical Studies Ltd, 6066 Leesburg Pike, 6th Floor, Falls Church, Virginia 22041, USA
[2] Mt. Sinai School of Medicine, New York, USA
[3] Little Rock, Arizona, USA
[4] Pfizer Pharmaceuticals Group, New York, USA

The objective of this study was to investigate switching patients with schizophrenia, who required a change in medication due to inadequate efficacy or unacceptable side effects, from olanzapine to ziprasidone.

This was an interim analysis of a randomized, blinded-rater study in which stable outpatients **(**n=58**)** discontinued olanzapine and received ziprasidone 40–160 mg/day for 6 weeks. Standard psychopathology rating scales and a cognitive battery were administered as part of the clinical assessment.

After 6 weeks of treatment, there were significant reductions in PANSS total, and the PANSS positive and negative subscale scores as well as the CGI-severity score ($P<0.05$). Almost half the patients were rated as improved on the CGI and only 5% discontinued due to insufficient response. Significant improvements were seen in verbal learning and memory. Mean baseline movement disorder assessment scales scores and anticholinergic use were very low and remained so on ziprasidone treatment. Treatment-emergent extrapyramidal side-effects were very rare. Mean body weight decreased significantly and median cholesterol, and triglyceride levels decreased.

Patients who may require a change from olanzapine therapy appear to benefit from switching to ziprasidone. Symptoms improved in many patients and ziprasidone was well tolerated. The significant improvement in verbal learning and memory, a key domain of cognitive function, on ziprasidone is noteworthy as this may be linked with functional outcome. Beneficial changes in markers of health status after just 6 weeks of ziprasidone therapy are also noteworthy.

Poster No. 86

A 28-Week Comparison of Ziprasidone and Haloperidol in Outpatients with Stable Schizophrenia

Rory O'Connor M.D.,[1] Steven Hirsch, M.D.,[2] Aidan Power, M.D.[3]

[1] Pfizer Pharmaceuticals Group, New York, USA
[2] Imperial College School of Medicine, London, UK
[3] Pfizer Limited, Sandwich, Kent, UK

This randomized, double-blind study was undertaken to compare flexible-dose oral ziprasidone 80–160 mg/day (*n*=148) with haloperidol 5–15 mg/day (*n*=153) over 28 weeks in outpatients with stable chronic or subchronic schizophrenia.

Patients with a baseline PANSS negative subscale score ≥ 10 and a GAF score >30 were assessed using the PANSS, CGI-S, MADRS, Simpson–Angus, Barnes Akathisia, and AIMS scales.

Modal doses at endpoint were 80 mg/day and 5 mg/day for ziprasidone and haloperidol, respectively. Robust improvements in all efficacy variables with both ziprasidone and haloperidol were observed. The percentage of patients classified as PANSS negative symptom responders at endpoint (≥ 20% reduction) was significantly greater with ziprasidone compared with haloperidol (48% vs 32%; $P<0.05$). A trend for greater efficacy in improving depressive symptoms was also observed with ziprasidone. Ziprasidone was associated with fewer adverse events and discontinuations than haloperidol. Ziprasidone had clear advantages over haloperidol in all evaluations of movement disorders. Changes in body weight were negligible with both treatments.

Ziprasidone and haloperidol were both effective in reducing overall psychopathology. Ziprasidone was superior in the treatment of negative symptoms and was better tolerated than haloperidol. Thus, ziprasidone appears to offer a superior alternative to haloperidol in the medium-term treatment of stable outpatients.

Poster No. 87

Differing Side Effect Burden with Newer Antipsychotics

Peter Weiden, M.D.,[1] Joan Mackell, Ph.D.,[2]

[1] St Luke's/Roosevelt Hospital, Columbia University College of Physicians & Surgeons, 411 West
114th Street, Suite 3C, New York, NY 10025, USA
[2] Pfizer Pharmaceuticals Group, New York, USA

The objective of this study was to compare the side effect profiles between patients on conventional and newer "atypical" antipsychotics.

A self-administered survey was mailed in June 1998 to persons with schizophrenia, identified through NAMI and NMHA chapters. Data included demographic, treatment variables, and structured side effect variables: tremor, weight gain, sedation, and sexual dysfunction.

Most of the 253 respondents (71%) were receiving an atypical antipsychotic – clozapine, risperidone, olanzapine, quetiapine. The group on conventionals reported more problems with tremors than those on atypicals both in frequency (12% versus 7%, $P = .14$), and distress (16% versus 7%, $P = .06$). In contrast, patients on atypicals were more likely to report weight gain (34% versus 16%, $P < .01$), sedation (29% versus 8%, $P < .001$), and sexual dysfunction (19% versus 14%, $P = .32$). These differences could not be accounted for by covarying baseline differences. Women reported a significantly higher frequency of weight gain than men (39% versus 22%, $P < .01$) along with greater distress (53% versus 25%, $P < .001$).

Self-reported side effect profiles diverge between older and newer antipsychotics. Based on patient report, clinicians should shift emphasis from EPS, focusing more on weight gain, sedation, and sexual dysfunction.

Poster No. 88

Effect of Chronic Olanzapine Treatment on the Course of Presumptive Tardive Dyskinesia

Bruce Kinon, Bruce Basson, Denai Milton, Virginia Stauffer

Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285

Objectives: Novel antipsychotic drugs may offer a treatment for tardive dyskinesia (TD). In preliminary studies, clozapine as well as olanzapine (OLZ) have demonstrated a reduction of TD symptoms that improves over weeks to months (Lieberman et al. 1991; Littrell et al. 1998; O'Brien and Barber 1998). The effect of OLZ on reducing the symptoms of presumptive TD was investigated in a large clinical trial database out to 30 weeks.

Methods: Patients (N=129) with presumptive TD were identified from three controlled multi-center clinical trials (HGAD, E003, HGAJ) that investigated the efficacy and safety of olanzapine treatment (2.5-20 mg/day; double-blind) of schizophrenia for up to 52 weeks. Presumptive TD was defined as a severity rating of moderate in at least one of seven body regions assessed with the Abnormal Involuntary Movement Scale (AIMS) at 2 consecutive drug-free baseline visits (2-9 days apart). Patients were rated weekly for the initial 6 weeks of OLZ treatment and then every 2 to 8 weeks thereafter depending on the study. Analysis included patients treated up to 30 weeks.

Results: Mean AIMS Total scores (items 1-7) were determined at each visit. The baseline (Week 0) mean AIMS Total was 10.55. The mean AIMS Total was significantly reduced from baseline by Week 1 and remained significantly lower at all subsequent assessments ($p<0.05$ for all weeks; within-group; signed-rank test). Mean reductions of 55% and 71% were noted at Week 6 and 30, respectively.

Conclusions: Retrospective analysis of patients with presumptive TD entering an OLZ clinical trial demonstrates a significant reduction of mean AIMS Total scores. The marked and persistent effect for up to at least 30 weeks suggests that OLZ may contribute to the improvement of TD through a mechanism other than neuroleptic masking of symptoms.

This study was funded by Eli Lilly and Company.

Poster No. 89

The Comparative Anti-Muscarinic-Like Adverse Event Profiles of Olanzapine and Risperidone Treatment in Patients with Schizophrenia Spectrum Psychosis

John Kennedy, M.D.; Bruce Basson, M.S.; Peter Tran, M.D.; Charles Beasley Jr., M.D.; Frank Bymaster, M.S.; Alan Breier, M.D.

Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285

Hypothesis: That affinity differences between olanzapine (OLZ) and risperidone (RISP) would be reflected in objective, peripheral antimuscarinic-like (A-M-L) adverse events. Change in PANSS Thought subfactor (PTS) score was evaluated to determine if doses effective in reducing thought disturbance had been employed.
Methods: Double-blind, randomized trial of OLZ versus RISP in 339 patients aged 18-65 with schizophrenia spectrum acute psychosis.
Results: Mean PTS for both treatments improved over time, with a trend toward more significant improvement with OLZ-treated patients ($p = 0.069$). Frequencies of treatment-emergent A-M-L events were: dry mouth (OLZ=22.2%), RISP=20.6%, $p = 0.731$); constipation (OLZ=9.6%; RISP=9.7%, $p = 0.971$); blurred vision (OLZ=9.6%, RISP=20.6%, $p = 0.005$); and micturition difficulties (OLZ=3.6%, RISP=5.5%, $p = .414$). Proportion experiencing at least one of these four events was: OLZ=32.9%, RISP=37.6%, $p=0.376$). At week one, proportion experiencing at least one treatment-emergent A-M-L event was higher in the RISP group than in the OLZ group (23.0% vs 13.8%, $p=0.029$).
Conclusion: The incidence of anti-muscarinic-like effects seen with OLZ was comparable to that seen with RISP treatment, suggesting that the compounds' in vitro muscarinic K_i's do not predict in vivo effects at clinical doses which are associated with a reduction in thought disturbance.

This study was funded by Eli Lilly and Company.

Poster No. 90

Average Dose and Weight: Olanzapine vs. Risperidone

James M. Russell, M.D.,[1] Joan A. Mackell, Ph.D.,[2] and James M. Martinez, M.D.[1]

[1] The University of Texas Medical Branch at Galveston, 404 University Boulevard, Rebecca Sealy Suite 4.510, Galveston TX 77555-0191
[2] Pfizer, Inc., New York NY

Introduction: Weight gain, associated with the administration of many antipsychotic medications, increases the risk of medical comorbidity and mortality, and is a major contributor to non-compliance.

Objective: This study evaluates average daily dose and weight gain in outpatients treated with either risperidone or olanzapine. The impact of baseline weight, Body Mass Index (BMI), daily dose, diagnosis, comorbid medical conditions, concomitant medications, age and gender is also examined.

Methods: Charts were randomly selected from an outpatient community mental health center to include patients prescribed olanzapine or risperidone for at least six months with 80% compliance. Diagnosis and symptom severity were confirmed by SCID and SLC-90 during a follow-up interview.

Results: Sixty individuals (31 males) met inclusion criteria. The mean age was 42.7 for olanzapine and 43.2 years for risperidone patients. The mean baseline BMI was 29.9 for olanzapine and 28.5 for risperidone patients. The mean (SD) change in BMI was 6.4% (11.4%) for olanzapine and 4.1% (10.0%) for risperidone patients. On average, patients were treated with 18.6 mg/day of olanzapine and 5.5 mg/day of risperidone for 18 months. After adjusting for the published recommended daily dose, olanzapine patients were more likely to be treated with higher doses ($p < 0.001$). There was a significant correlation between mean daily dose and percent increase in BMI.

Conclusion: Both olanzapine and risperidone were frequently associated with weight gain. After adjusting for confounds, patients treated with high doses of olanzapine were most likely to have significant increases in weight. While health and compliance consequences of weight gain have been reported elsewhere, further study is required to determine the effects of observed weight gain in this cohort.

Supported by an Unrestricted Grant from Pfizer, Inc

Poster No. 91

DIFFERENCES IN PLATELET PAROXETINE BINDING TO 5-HT UPTAKE SITES IN AGITATED AND NON-AGITATED ALZHEIMER'S DISEASE PATIENTS

Jacobo Mintzer, MD, Dario Mirski, MD, David Knight,BS *, Mike Owens, BS*, Karin Barkin, MD, Marilyn Stuckey, BSN, RN, Heather Duncan, BS, CMC

Medical University of South Carolina, Department of Psychiatry, 67 President Street, P.O.Box 250861, Charleston, S.C. 29425
*Emory University, Department of Psychiatry, Atlanta, GA

Introduction: Currently a large body of literature supports the relationship between aggression and serotoninergic dysfunction. Furthermore, patients with Alzheimer's Disease (AD) have well-established findings regarding pathology in the serotoninergic system at the Central Nervous System level (Andersson et al. 1991). Ours (Mintzer et al 1998) and others (Lanctot et al 1997) challenge data supports the presence of serotoninergic dysfunction in agitated (Mintzer et al 1998) and agitated/aggressive AD patients (Lanctot et al 1997). It is; however, unknown if this is a state phenomenon secondary to an AD related process or a trait that is manifested in predisposed AD patients. This study addresses this issue by assessing 5-HT Uptake Sites in aggressive and non-aggressive AD patients' platelets an organ not known to be affected by the primary AD process. Objective**:** Explore possible differences, specifically in binding affinity (Kd) and maximum number of binding sites (Bmax), in 5-Ht Uptake sites in platelets between, patients with AD, AD with behavioral disturbances and age matched normal control subjects using [^{3}H] Paroxetine Platelet Binding. Methods: We recruited 14 patients suffering from AD (6 with aggressive behavior and 8 without aggression) and 6 elderly normal controls. All subjects were objectively rated for cognitive function (MMSE), Depression (CDS), and Agitation/Aggression (CMAI). Blood samples and paroxetine binding was performed according to Andersson et al, 1991 procedures. Results: We recruited 6 patients in the AD aggression group (3m and 3f) mean age 76.7 (+/- 10.7), 8 patients in the non-aggressive group (1m and 7f) mean age 83.1 (+/-5.6) and 6 non-demented normal controls (3m and 3f) mean age 71.5 (+/-4.3). Binding affinity (AD with aggression 0.14 nM +/- 0.02 vs. AD without aggression 0.21 nM +/- 0.08) was significantly ($p<0.05$) lower for the aggressive when compared to the non-aggressive AD patients. The Maximum Number of binding sites (Bmax) was higher for the AD aggressive group (2269 fmol/mg +/- 419) than for the non-aggressive AD group (1957 fmol/mg +/- 615), but those differences were not statistically significant. Normal elderly controls showed no statistical differences with either group in Kd (0.16 nM +/- 0.6) or Bmax (2341 fmol/mg +/-283). Conclusion: These findings although preliminary tend to support the notion of a serotoninergic dysfunction in AD aggressive patients. Further these results suggest this dysfunction to be at least in part due to trait tendencies. We are currently obtaining in depth information about patient's personality traits before the onset of AD in order to further evaluate our findings.

Poster No. 92

A Weight Management Program for Treatment of Olanzapine Related Weight Gain

M. Patricia Ball, R.N.C.M.S., Vanessa Coons, and Robert W. Buchanan, M.D.

Maryland Psychiatric Research Center, P.O. Box 21247, Catonsville, MD 21228.

Background: In the course of conducting the study, "Olanzapine in Treatment–Resistant Schizophrenic Outpatients," it has become apparent that a significant number of patients gain weight while taking olanzapine. A review of the literature verifies this finding in other clinic populations. Since obesity is a known medical risk factor, is detrimental to a person's self-esteem, and becomes a compliance issue since many patients who are quite distressed by weight gain may elect to stop taking their medication, it seemed beneficial to determine if this side effect could be treated. To date, there have been no controlled studies of possible weight loss strategies with this population. The aim of this study is to determine if an accepted and proven weight loss program, such as Weight Watchers, would be successful in helping patients who have olanzapine-related weight gain to lose weight. In addition to learning whether patients can lose weight, it may be possible to learn something about which factors predict program success.

Methods: Patients have been recruited from the Maryland Psychiatric Research Center (MPRC) Outpatient Research Program, MPRC Schizophrenia and Related Disorders Program, and Way Station Psychosocial Program. All patients have been on olanzapine for at least 6 months and experienced a significant weight gain since beginning treatment with olanzapine. Patients have been screened for the presence of other factors which may have accounted for their weight gain and only patients whose weight gain can be documented to be secondary to treatment with olanzapine have been admitted to the study. Patients' weight gain has been documented as exceeding recommended guidelines for age, sex, and body type. Weight Watchers is providing an 11 week education and support group. The group leader is working with the senior research nurse (MPB) to assure the format is adjusted to meet the needs of people who have chronic schizophrenia without altering the basic content of the program. Care providers are monitoring patient diets and an exercise program is being supervised by the senior research nurse and a student intern (VC). Exercise sessions are planned 3 times a week. All participants have received medical clearance, including chemistry profile, CBC, thyroid function tests, urinalysis, pregnancy test for women, EKG, height/weight, body mass index, and clinical ratings (BPRS, SANS, Hamilton, and CGI). Weight is monitored weekly and all other ratings will be repeated at the end of the 11 week program.

Results: The study is scheduled to conclude April 15, 1999. Twenty-one patients were recruited for the study. By the end of week 3, ten patients had withdrawn for various reasons. Of the eleven remaining patients, eight have participated in the supervised exercise program at MPRC Outpatient Research Program, and all attended weekly Weight Watchers group meetings. A preliminary analysis of the data has been done using Repeated Measures Analysis of Variance (RM-ANOVA). Variables used for the analysis were weight, sex, and exercise. Mean weight loss

was 5.2 pounds, significant at 0.05. Mean weight loss for the males (n=7) was 6.9 pounds, which is significant at the 0.05 level. Mean weight loss for the females (n=4) was 2.5 pounds, which was not significant. There was no correlation between exercise and weight loss. However, patients have significantly increased their level and length of exercise and this may correlate with BMI measurements which will be completed after the final session. The final analysis will also include comparison to a matched control group of patients who have not participated in this program. Symptom ratings will also be included in that analysis. Results so far seem to justify an extension of the trial to maximize significant results.

This study has been supported by a grant from Eli Lilly and Company.

Poster No. 93

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Poster No. 94

Cognitive Effect of Olanzapine in Schizophrenic Patients

Ileana Berman[1,2], David Klegon[1], Roger Bayog[1,2], Catherine Chmiel[2] , Howard H. Chang[1,2]

1) Consolidated Department of Psychiatry, Harvard Medical School
2) Taunton State Hospital, 60 Hodges Ave, Taunton MA 02780

Introduction: There is evidence suggesting that, compared to typical antipsychotics the atypical neuroleptics such as clozapine and risperidone have a superior cognitive effect. We are presenting the outcome findings in a long term care psychiatric hospital about the effect of olanzapine (OLZ) on cognitive function in a group of patients with schizophrenia or schizoaffective disorder.

Method: We assessed a group of 20 patients who met DSM IV diagnostic criteria for schizophrenia and schizoaffective disorder, before and approximately six weeks after the initiation of OLZ. The assessments included the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) and a cognitive battery consisted of tests of attention, visual and auditory memory, and executive function. We performed t-test analysis to compare the baseline with the final assessments.

Results: Patients improved significantly on the positive symptom subscale of the PANSS ($p=0.02$, $n=20$) and scored better on the global cognitive measure as indicated by the Mini-Mental Status Examination ($p=0.052$, $n=20$). Our results are similar to the earlier findings we obtained in a similar group of patients treated with risperidone. We compared the cognitive effect of OLZ with that of risperidone using analyses of variance having baseline scores as covariates. There were no statistically significant group differences in any of the cognitive measures we assessed.

Conclusions: This suggests that, despite the strong anticholinergic properties, olanzapine had cognitive effect that resembled in many ways that of risperidone.

Poster No. 95

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Poster No. 96

DIFFERENCES IN PLATELET PAROXETINE BINDING TO 5-HT UPTAKE SITES IN AGITATED AND NON-AGITATED ALZHEIMER'S DISEASE PATIENTS

Jacobo Mintzer, MD, Dario Mirski, MD, David Knight,BS *, Mike Owens, BS*, Karin Barkin, MD, Marilyn Stuckey, BSN, RN, Heather Duncan, BS, CMC

Medical University of South Carolina, Department of Psychiatry, 67 President Street, P.O.Box 250861, Charleston, S.C. 29425
*Emory University, Department of Psychiatry, Atlanta, GA

Introduction: Currently a large body of literature supports the relationship between aggression and serotoninergic dysfunction. Furthermore, patients with Alzheimer's Disease (AD) have well-established findings regarding pathology in the serotoninergic system at the Central Nervous System level (Andersson et al. 1991). Ours (Mintzer et al 1998) and others (Lanctot et al 1997) challenge data supports the presence of serotoninergic dysfunction in agitated (Mintzer et al 1998) and agitated/aggressive AD patients (Lanctot et al 1997). It is; however, unknown if this is a state phenomenon secondary to an AD related process or a trait that is manifested in predisposed AD patients. This study addresses this issue by assessing 5-HT Uptake Sites in aggressive and non-aggressive AD patients' platelets an organ not known to be affected by the primary AD process. Objective**:** Explore possible differences, specifically in binding affinity (Kd) and maximum number of binding sites (Bmax), in 5-Ht Uptake sites in platelets between, patients with AD, AD with behavioral disturbances and age matched normal control subjects using [^{3}H] Paroxetine Platelet Binding. Methods: We recruited 14 patients suffering from AD (6 with aggressive behavior and 8 without aggression) and 6 elderly normal controls. All subjects were objectively rated for cognitive function (MMSE), Depression (CDS), and Agitation/Aggression (CMAI). Blood samples and paroxetine binding was performed according to Andersson et al, 1991 procedures. Results: We recruited 6 patients in the AD aggression group (3m and 3f) mean age 76.7 (+/- 10.7), 8 patients in the non-aggressive group (1m and 7f) mean age 83.1 (+/-5.6) and 6 non-demented normal controls (3m and 3f) mean age 71.5 (+/-4.3). Binding affinity (AD with aggression 0.14 nM +/- 0.02 vs. AD without aggression 0.21 nM +/- 0.08) was significantly ($p<0.05$) lower for the aggressive when compared to the non-aggressive AD patients. The Maximum Number of binding sites (Bmax) was higher for the AD aggressive group (2269 fmol/mg +/- 419) than for the non-aggressive AD group (1957 fmol/mg +/- 615), but those differences were not statistically significant. Normal elderly controls showed no statistical differences with either group in Kd (0.16 nM +/- 0.6) or Bmax (2341 fmol/mg +/-283). Conclusion: These findings although preliminary tend to support the notion of a serotoninergic dysfunction in AD aggressive patients. Further these results suggest this dysfunction to be at least in part due to trait tendencies. We are currently obtaining in depth information about patient's personality traits before the onset of AD in order to further evaluate our findings.

Poster No. 97

Factors Influencing Change in ADAS-Cog Scores in Patients with Mild to Moderate Alzheimer's Disease: Perspectives from Multinational Placebo Controlled Trials.

Kevin Bellew BS[1], Katherine Beebe PhD[1], James McCafferty BS[1], Matthew Truman MSc[2], and Rajinder Kumar MD[1].

1. SmithKline Beecham Pharmaceuticals, Neuroscience Therapeutic Unit, Collegeville PA 19426, 2. SmithKline Beecham Pharmaceuticals, Biostatistics and Data Sciences, Harlow, UK

Background: The ADAS-Cog is a neuropsychological instrument (1) widely used to measure cognitive change in antidementia drug trials. Positive findings with approved therapies were based on small cognitive enhancement seen in the treated groups relative to modest deterioration in the placebo patients. Accordingly, the rate of decline in placebo patients is important in interpreting clinical trial results. This analysis examined the influence of variables on cognitive change in patients with mild to moderate AD who received placebo for six months in multinational clinical trials. Patients were tested up to four times during the treatment period.

Methods: A multiple regression model was used to examine eleven clinically relevant covariates in a cohort of over 800 patients. These included cognitive status (MMSE), baseline ADAS score, age, gender, APOE4, and therapies thought to influence the clinical course of AD such as smoking, HRT and use of anti-inflammatory drugs. MMSE at intake was 12-24. The average age was 74 years, 61% were females and 36% reported taking anti-inflammatory therapies.

Results: The average rate of decline was 1.7 points on the ADAS-Cog over six months or an annualized rate of 3.4 points. Covariate analysis showed that mental status as measured by the MMSE was inversely associated with an increase in the ADAS-Cog score (i.e. deterioration in cognition). The use of anti-inflammatory drugs was also associated with an increase in ADAS-Cog score. The latter finding was consistent across countries and across studies in which the use of anti-inflammatory drugs was greater than 20% of the population. There was a small but significant contribution from age. Baseline ADAS-Cog was not a significant predictor. The total contribution for all variables included in the model was relatively small as evidenced by an R^2 value of approximately 5%.

Covariate	Estimate	Standard Error	P-Values	Cumulative R^2
MMSE	-0.302	0.0586	0.0001	0.0305
Anti-inflammatory Use	+1.364	0.446	0.0023	0.0411
Age	-0.0681	0.024	0.0048	0.0502
All Other Variables	-	-	-	0.0507

ADAS-Cog Δ = 12.1 - 0.31 x MMSE - 0.07 x Age + 1.4 x AIN
(MMSE at screening, age in years, AIN = 1 for anti-inflammatory drug use and 0 otherwise)

Conclusion: These results suggest that the rate of cognitive decline in mild to moderate AD patients in clinical trials of short duration as measured by the ADAS-Cog is slow. The present findings also suggest that the rate of decline is influenced by only a few variables, and the overall magnitude of this effect is small. The findings that the use of anti-inflammatory drugs is associated with decreased cognitive function warrants further investigation.

References:
(1) Rosen et al. Am. J. Psychiatry, 1984

Poster No. 98

Olanzapine Reduces Psychosis and Behavioral Disturbances Associated with Alzheimer's Disease

Jamie Street, MD; W. Scott Clark, PhD; Kimberley S. Gannon, PhD; Steve Mitan, MS; Deborah Kadam, MA; Todd Sanger, PhD; Roy Tamura, PhD; Gary D. Tollefson, MD, PhD

Eli Lilly and Company, Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN 46285

A multicenter, double-blind, placebo-controlled study was conducted in nursing home patients with moderate to severe dementia to determine the efficacy and safety of olanzapine in the treatment of psychotic symptoms and behavioral disturbances associated with Alzheimer's disease. Subjects met the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for possible or probable Alzheimer's disease. The efficacy of olanzapine compared with placebo in the treatment of psychosis and behavioral disturbances was measured by changes in the mean scores from baseline to endpoint on the Neuropsychiatric Inventory - Nursing Home version (NPI/NH), a caregiver-rated scale that assesses psychopathology in dementia. Following a placebo lead-in period, 206 patients were randomly assigned to either placebo or a fixed dose of 5 mg, 10 mg, or 15 mg/day of olanzapine for up to 6 weeks of double-blind therapy. Efficacy and safety were evaluated at weekly intervals.

Olanzapine (5 mg/day and 10 mg/day) provided superior efficacy compared to placebo on the combined Delusions and Hallucinations items of the NPI/NH ($p=.001$ and $p=.037$, respectively). A significantly greater improvement on the Agitation/Aggression item of the NPI/NH occurred in those patients treated with 5 mg/day or 10 mg/day of olanzapine compared to placebo ($p=.014$ and $p=.018$, respectively). The proportion of patients exhibiting a 50% or greater improvement in symptoms as measured by the NPI/NH combined Agitation/Aggression, Delusions and Hallucinations items was greater for patients treated with 5 mg/day (65.5%, $p=.005$) or 10 mg/day (57.1%, $p=.041$) of olanzapine compared to placebo (35.6%). A slight improvement (ns) in cognitive functioning (MMSE) was evident for those patients treated with 5 mg/day of olanzapine. No significant changes in extrapyramidal side effects were found for patients treated with olanzapine compared to placebo.

Poster No. 99

Preliminary Evaluation of AIT-082 in Patients with Alzheimer's Disease

Steven D. Targum, M.D.[1], Scott Wieland, Ph.D.[2], Michelle S. Glasky, Ph.D.[2], and Alvin J. Glasky, Ph.D.[2]

[1] Clinical Studies, Philadelphia, 400 Market Street, Suite 425, Philadelphia, PA 19106
[2] NeoTherapeutics, 157 Technology Dr., Irvine, CA 92618

Alzheimer's disease is a progressive illness in which memory loss is a core symptom ultimately affecting both behavioral and social function. AIT-082 is a derivative of the purine hypoxanthine containing a para-aminobenzoic acid moiety that appears to be a "neurotrophic" agent that may benefit patients with Alzheimer's disease. AIT-082 has a low potential for toxicity and rapidly passes through the blood-brain barrier. Further, AIT-082 has demonstrated positive effects on working memory in animal studies and has revealed excellent safety and tolerance in three phase 1 clinical studies.

The present phase 2 study assessed the safety characteristics and efficacy of AIT-082 administered for 28 days to patients meeting DSM-IV/ADRDA criteria for mild to moderate senile dementia of the Alzheimer's type (SDAT). There were 13 sites in the trial representing Clinical Studies, Ltd., who oversaw the recruitment and operations of the study. Seventy four patients (and caregivers) consented to participate in this multi-center, randomized, double-blind, placebo-controlled, parallel design evaluation of AIT-082 50mg (n=17), 150mg (n=18), 500mg (n=16), or placebo (n=16) taken once daily in liquid suspension in the morning. Assessments included the ADAS-cog, CIBIC-plus, Behave-AD, Activities of Daily Living (ADL), Dysfunctional Behavior Rating instrument (DBRI), safety laboratory tests, ECG, and adverse event monitoring.

Results revealed an improvement from baseline measures in mean total ADAS-cog scores at all dose levels and a slight decrement in the placebo group after 28 days administration of AIT-082 (ANOVA, F=2.49, df=3, p=0.068). Total ADAS-cog scores improved in 59% of patients receiving AIT-082 50 mg daily, 72% receiving 150 mg, 63% receiving 500 mg, and only 38% in the placebo group. The Global Behave-AD revealed significant differences between dose groups and placebo (ANOVA, F=2.88, df=3, p=0.043). There were no significant changes over 28 days in the CIBIC-plus, ADL, or DBRI. There were no significant adverse events or laboratory findings. AIT-082 was well tolerated and appeared to be safe at all doses.

These preliminary results suggest that AIT-082, a unique purine derivative, may have therapeutic benefit for patients with senile dementia of the Alzheimer's type. Larger studies of longer duration are needed to ascertain the sustained cognitive benefit of AIT-082 in affecting the progression of Alzheimer's disease.

***Sponsored by NeoTherapeutics, Irvine, California**

Poster No. 100

Centrally Acting Antiemetics Reduce Gastrointestinal Side Effects In Alzheimer's Patients Receiving The Cholinesterase Inhibitor Rivastigmine (Exelon ®, SDZ ENA 713)

Neal R. Cutler, MD,[1] Ravi Anand, MD,[2] Richard D. Hartman, PhD,[2] John C. Messina Jr., PharmD,[2] Stanford S. Jhee, PharmD,[1] John J. Sramek, PharmD.[1]

[1]California Clinical Trials, 8500 Wilshire Blvd., 7th floor, Beverly Hills, CA
[2]Novartis Pharmaceuticals Corporation, East Hanover, NJ

Cholinesterase inhibitors used for the treatment of Alzheimer's disease frequently cause dose-related nausea and vomiting. This prospective, randomized, open-label pilot study was designed to evaluate the efficacy of four antiemetic treatments during a four-week forced dose escalation of rivastigmine from 3mg/d to 12mg/d in patients with Alzheimer's disease. Twenty-six of 82 enrolled patients experienced dose-related nausea and/or vomiting requiring antiemetic treatment. Patients were rated on the Emetic Process Rating Scale (EPRS) every 4h and the Clinical Global Impression (CGI) scale at 72h. Treatment success was defined as a CGI score of $\leq$ 2. Glycopyrrolate 1 mg (n=3) had a 33% success rate, ondansetron 4 mg (n=4) had a 50% success rate, trimethobenzamide 250 mg (n=9) had an 89% success rate, and trihexyphenidyl 2 mg (n=10) had a 90% success rate. Glycopyrrolate, an anticholineric compound, and ondansetron, an antiserotonergic compound, are both primarily peripherally acting antiemetics. In contrast, both trimethobenzamide, which is thought to act on the chemoreceptor trigger zone, and trihexyphenidyl, an anticholinergic compound, act via central mechanisms. Thus, centrally acting antiemetic compounds were effective in preventing nausea and vomiting with rivastigmine, indicating that these effects are centrally mediated.

This study was supported by Novartis Pharmaceuticals Corp.

Poster No. 101

SIDE EFFECTS AND TIME COURSE OF RESPONSE IN A PLACEBO-CONTROLLED TRIAL OF FLUOXETINE IN GERIATRIC DEPRESSION

Deborah L. Ackerman, M.S., Ph.D.[1]; Sander Greenland, M.S., Dr.P.H.[1]; Alexander Bystritsky, M.D. [2]; Gary W. Small, M.D.[2,3,4]

[1]Department of Epidemiology, UCLA School of Public Health, Box 951772, Los Angeles, CA, 90095-1772
[2]Department of Psychiatry and Biobehavioral Sciences, UCLA Neuropsychiatric Institute, Los Angeles, CA

The often high placebo response rate can complicate the evaluation of true drug effect in controlled clinical trials. We reanalyzed data from a large, multicenter, placebo-controlled clinical trial of fluoxetine treatment of geriatric depression to evaluate similarities and differences between responders and nonresponders in both treatment groups. Fluoxetine was superior to placebo on all outcome measures, but response rates varied across sites. Clinical differences in the patient populations may have contributed to the different response rates.

We used Mantel-Haenszel tabular methods and multinomial (polytomous) logistic regression to examine (1) clinical differences among the 671 patients at the 30 sites, (2) side effects as possible predictors of response and of drop-out, and (3) the time course and onset of response.

We found that larger sites had higher response rates: Patients at larger sites tended to have less severe depression as measured by the CGI and the GDR, more severe depression as measured by the HAMD21, higher cognitive disturbance scores, and lower psychomotor retardation scores.

Among somatic complaints associated with fluoxetine response, headache before and after randomization was associated with good response; and constipation and anxiety after randomization were associated with poor response. Somnolence before and after randomization was associated with good placebo response.

Early and persistent improvement occurred among similar proportions of responders in both groups. The difference between fluoxetine and placebo appeared to be a persistent response beginning during the 4th week. Pretreatment somnolence was associated with early, persistent improvement in both groups, and may serve as a marker for placebo response.

Further evaluation of the common symptoms of depression, their interaction with the natural course of illness, and with drug treatment could determine whether these symptoms can be used by clinicians to guide treatment.

This work was supported by NIMH grant MH-53935.

Poster No. 102

The Effect of Bupropion SR on the Quality of Life of Elderly Depressed Patients with Medical Illnesses

Molly Fortner, B.S.[1], Indu Varia, M.D.[2], Ken Gersing, M.D.[3], and P. Murali Doraiswamy, M.D.[4]

[1-4]Duke University Medical Center, Box 3018, Durham, North Carolina, 27710.

There is an increased prevalence of depression in elderly patients with serious medical illnesses. Untreated depression is often associated with a lower quality of life and increased disability in such patients. There is little data, however, on the effects of acute antidepressant therapy on functional health and well-being in this subset of the population. In this report we describe interim results from an ongoing study evaluating the effects of antidepressant therapy on depression ratings and quality of life measures in elderly medically ill patients.

Eighteen subjects, ranging from 61 to 80 years (mean age $\pm$ SE = 69.9 $\pm$ 1.3 years), were enrolled after written informed consent. All subjects met DSM-IV criteria for major depression (mean HAM-D total = 18.3 $\pm$ 1.0) and the mean Cumulative Illness Rating Scale (CIRS-G) was 12.2 $\pm$ 1.2. Examples of these patients' comorbid medical conditions included serious congestive heart failure, coronary artery disease, chronic obstructive pulmonary disease, and insulin-dependent diabetes. Efficacy was measured by changes in scores on the SF-36 at week 12 and the 17-item HAM-D and Clinical Global Impressions for Improvement of Illness (CGI-I) scale at week 8. Bupropion SR (Wellbutrin SR) therapy was initiated at 100 mg po qd and titrated according to the patient's tolerability to a maximum dose of 150 mg po bid (mean = 222 $\pm$ 18 mg.)

By endpoint (LOCF), bupropion SR treatment reduced depressive symptoms as indicated by the HAM-D total score and the CGI-I ($p < 0.05$). The individual HAM-D items that changed significantly were "depressed mood," "feelings of guilt," "insomnia late," "work and activities," and "hypochondriasis" ($p < 0.05$). On the SF-36, the items "social functioning," "vitality," and "mental health" improved significantly from baseline to week 12 ($p < 0.05$). Four subjects dropped out due to adverse events ($n = 2$) or other reasons ($n = 2$).

These pilot data demonstrate that bupropion SR is relatively well tolerated and may improve both depression and quality of life in elderly depression patients with multiple medical illnesses. A randomized placebo-controlled study is warranted to confirm these findings.

Acknowledgement: Supported by a grant from Glaxo Wellcome Inc.

Poster No. 103

Acoustic Measures of Speech in Geriatric Depression Treated with Sertraline or Nortriptyline.

Murray Alpert, Ph.D.[1] Raul R. Silva, M.D.[2] and Enrique R. Pouget[1]

[1]Department of Psychiatry, HN 323, NYU Medical Center, 550 First Ave. NY, NY, 10016.
[2] St. Lukes/Roosevelt Hospital Center, 411 W. 144th St., N.Y., N.Y.

Paralinguistic measures of a depressed patient's speech can inform the clinician about various aspects of the patient's condition. Previous studies have examined automatic speech, such as counting or reading or free speech. We have explored the potential for adding acoustic measures of the patients' speech as an outcome measure in treatment trials since paralinguistic aspects of the patients' free speech can inform the clinician about the patients' condition. A number of speech measures, involving both timing and prosody, have been reported as relevant for our purpose and we here report systemic study of measures that correlate with clinical ratings, measures that change with effective treatment, and the statistical power of acoustic measures in a clinical trial. Recordings were done at baseline and outcome in a trial comparing sertraline and nortriptyline in patients with geriatric depression. A group of age matched controls were also recorded in parallel with the treatment groups.

The sample consisted of 22 evaluable patients (12 males, 10 females), aged 60 to 79 years, (mean=67.4 yr.). All met DSM-III-R (1985) criteria for Major Depressive Disorder, without psychotic features. Patients were randomized to either sertraline, 50 to 150 mg/day (N=12) or nortriptyline, 50 to 100 mg/day (N=10) for up to 12 weeks following a 1 week placebo lead in. Efficacy was evaluated with the Ham-D and the BDI. The POMS is used to divide patients into retarded and agitated groups for the examination of speech timing. Recordings were done to coincide with the baseline and outcome ratings.

There was a highly significant reduction in Ham-D scores. The groups did not differ at baseline or outcome for Ham-D scores, but differed for BDI scores, suggesting differential subjective action. Productivity measures such as pausing and utterance duration, as well as measures of dyadic interaction, were related to depression severity measures at baseline and at outcome. The clinical ratings, on the whole, showed larger effect sizes but specific acoustic measures provide opportunities to examine individual behavioral sites of anti depressant drug action. The results are promising and it would be worthwhile to explore these relations in a larger sample. A battery of acoustic measures might provide a useful laboratory measure for the objective evaluation of clinically relevant behaviors.

Poster No. 104

Behavior Problems and the Risk of Institutionalization among Demented Elderly: Evidence from a Medicaid, Home and Community-Based Services (HCBSs) Program.

V. L. Phillips, D.Phil.[1] and Sadhna Diwan, Ph.D.[2]

[1] Department of Health Policy and Management, Rollins School of Public Health of Emory University, 1518 Clifton Road, Atlanta, Georgia 30322
[2] Department of Social Work, Georgia State University, Atlanta, Georgia

Background: Dementia is a known risk factor for nursing home placement. Behavioral problems associated with dementia are believed to increase further the likelihood of institutionalization as they increase caregiver burden. Little empirical evidence, however, exists to document the effect of behaviors on the risk of placement among demented elderly.

Medicaid agencies are a principle payer for long term care (LTC) in most states. Most now offer home and community-based services (HCBSs) with case management as an alternative to nursing home placement to eligible beneficiaries. These HCBS programs reduce the per person cost of LTC to the states. The purpose of this study is to examine the impact of behavior problems on the risk of institutionalization among demented elderly enrolled in a HCBS program in Georgia.

Methods: A random sample of 10% of clients discharged from the Community Care Services Program (CCSP) between August of 1995 and July of 1996 was collected from four regions in Georgia. Data on client demographics, living circumstances, activities of daily living (ADLs) and instrumental activities of daily living (IADLs), levels of formal and informal support, bowel and bladder continence, mental status, length of time in program, and reason for discharge were also collected. The presence of behavior problems and the time post enrollment that they emerged were also recorded.

For cognitively impaired clients, the time to institutionalization was analyzed using a Cox Proportional Hazards model with behavior as a time-varying covariate. Predisposing, enabling and illness-related factors were included as standard covariates. Those exiting the program for reasons other than nursing home placement were treated as censored observations.

Results: 37% (n=206) of clients were demented. Among this group 23% exhibited behavior problems and 43% were discharged to nursing homes. The mean age was 81 years, mean time in the program was 29 months, 72% of clients were female and 39% were African American. Exhibiting a behavior problem more than doubled the hazard ratio of placement (HR=2.71, p=0.000). Having more informal carers (HR=1.34, p=0.004) also significantly increased the likelihood of placement. Alternatively, being African American (HR=0.45, p=0.002) and female (HR=0.58, p=0.030) significantly reduced the likelihood of placement.

Significance: The identification of effective strategies, for example pharmacological, educational, and environmental, to offset the impact of problem behaviors should be pursued.

Poster No. 105

A Randomized Double-Blind Comparison Of Nortriptyline Plus Perphenazine Vs. Nortriptyline Plus Placebo In The Treatment Of Psychotic Depression In Late Life

Benoit H. Mulsant, M.D.[1, 2], Robert A. Sweet, M.D. [1, 2], Jules Rosen, M.D. [1, 2], Bruce G. Pollock, M.D., Ph.D. [1, 2], George S. Zubenko, M.D., Ph.D. [2], Charles F. Reynolds III, M.D. [1,2]

(1) Intervention Research Center for Late-Life Mood Disorders, University of Pittsburgh School of Medicine
(2) Western Psychiatric Institute and Clinic, 3811 O'Hara Street. Pittsburgh, PA 15213.
E-mail: mulsantbh@msx.upmc.edu

Background: In younger patients with psychotic depression, the rate of response to a combination of a tricyclic antidepressant plus a typical neuroleptic is almost twice as high as the rate of response to a tricyclic antidepressant alone. To our knowledge, no prospective randomized study has compared the efficacy of an antidepressant plus a neuroleptic vs. an antidepressant alone vs. in the treatment of psychotic depression in late life.
Methods: The efficacy of nortriptyline plus perphenazine vs. nortriptyline was compared in 36 older patients presenting with a major depressive episode with psychotic features. All patients were started openly on nortriptyline titrated to therapeutic levels (50-150 ng/ml) over two weeks. They were then randomized under double-blind conditions to addition of perphenazine (n=17) or placebo (n=19), titrated as tolerated up to 24 mg/day. Outcomes in the two treatment groups were compared.
Results: Both treatments were well tolerated with only one patient (5%) in each group dropping-out due to treatment side-effects. Thirty patients received nortriptyline for at least four weeks combined with either 8-24 mg/day of perphenazine (n=14) or placebo (n=16) for at least two weeks (median: 9 weeks; range: 2 to 16 weeks). There were no significant differences between the completers in the two treatment groups when comparing their scores on the Hamilton Rating Scale for Depression (11.4 ± 7.3 vs. 10.4 ± 7.3; p=0.68), the Brief Psychiatric Rating Scale (30.9 ± 10.7 vs. 31.7± 13.9; p=0.84), or any side-effects measure (all p's > 0.10). Rates of full response (defined as resolution of both depression and psychosis-- 50% vs. 44%), partial response (29% vs. 31%), and non-response (21% vs. 25%) were similar in the two groups (p=0.99).
Conclusion: When treating older patients with psychotic depression, the addition of a moderate dose of a traditional neuroleptic to a tricyclic antidepressant may not significantly improve efficacy. This result supports existing data suggesting that the pathophysiology (and thus the required treatment) of psychotic depression may be different early and late in life.

Supported by grants MH30915, MH49786, MH52247, MH01040, MH01153 and MH01613 from the National Institute of Mental Health

Poster No. 106

Clinical Improvement and Tolerability is Maintained Long Term in Elderly Patients with Psychotic Disorders Treated with Quetiapine

Paul Yeung, M.D.,[1] Pierre Tariot, M.D.,[2] Carl Salzman, M.D.,[3] Joseph Pultz, Ph.D.,[1] Joher Raniwalla, BSc, BM,[4] and Jeff Goldstein, Ph.D.[1]

[1]Zeneca Pharmaceuticals, Wilmington, DE 19850
[2]University of Rochester School of Medicine, Rochester, NY 14620
[3] Harvard School of Medicine, Boston, MA 02115
[4]Zeneca Pharmaceuticals, Alderley Park, UK

Physiologic changes can make elderly patients more vulnerable than younger patients to the side effects of standard antipsychotic medications, especially extrapyramidal symptoms (EPS). Quetiapine fumarate (quetiapine, SEROQUEL®), an antipsychotic with no treatment-emergent or dose-related EPS or elevations of plasma prolactin, has demonstrated advantages to suggest that it may be potentially a very attractive therapeutic option in an EPS sensitive patient population such as the elderly. To explore the therapeutic utility and tolerability of quetiapine in this EPS sensitive patient population, a 52-week, multicenter, open-label trial in men and women at least 65 years of age (50 years or older for patients with Parkinson's disease) with psychotic disorders was conducted. This report provides preliminary data in 184 patients regarding the clinical therapeutic utility and tolerability of quetiapine in elderly patients with psychotic disorders. Patients received 25 to 800 mg/day of quetiapine, dosed according to clinical response and tolerability for up to one year. Clinical benefit was assessed using the BPRS and the CGI. Patients were also evaluated using the Simpson-Angus Scale (SAS) and AIMS in addition to physical examinations, vital signs, weights, clinical laboratory tests, ECGs, and reports of adverse events. In this patient population with a mean age of 76 years, the median total daily dose was 100 mg and the median duration of exposure was 350 days. Significant improvement from baseline in BPRS Total ($p<0.0001$) and CGI Severity of Illness ($p<0.01$) scores was noted at all time points measured (from Weeks 2 onward). BPRS positive and negative symptom cluster scores also showed improvement at all time points. Clinically significant improvement, defined as a decrease of at least 20% from baseline scores on the BPRS, was achieved by 49% of the patients at end point. Mean SAS total score decreased from 19.0 at baseline to 17.2 at end point and the mean AIMS score decreased from 4.9 at baseline to 4.3 at end point. No clinically important effects on mean hematology or clinical chemistry values, ECGs, or vital signs were observed. The results from this open-label trial suggest that quetiapine may be an potential alternative to standard antipsychotic agents for long-term use in the elderly.

Supported by a grant from Zeneca Pharmaceuticals

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Poster No. 109

Efficacy of Sertraline in Long-Term Treatment in Panic Disorder: A Multicenter Study

Anita Clayton, M.D[1]., R. Bruce Lydiard, PhD., M.D.[2], Robert Wolkow, M.D[3], Arkady Rubin, PhD.[3],
Elizabeth Hackett, Ph.D.[3]

1. University of Virginia Department of Psychiatric Medicine, 2955 Ivy Road, Charlottesville, VA 22903
2. Medical University of South Carolina, Charleston, SC
3. Pfizer Inc., New York, NY

Objective: Panic Disorder often requires long-term treatment. Sertraline has been proven effective in several acute studies of Panic Disorder, with or without agoraphobia. The current study was undertaken to evaluate long-term efficacy and safety of sertraline treatment in Panic Disorder.

Methods: Outpatients with DSM III-R Panic Disorder who had completed one of 3 double-blind, placebo-controlled 10-week studies were treated for 52 weeks with open-label sertraline followed by randomization of responders (CGI-Improvement of 1 or 2) to 28 weeks of double-blind, placebo-controlled treatment. Efficacy was evaluated by number, intensity and duration of full-blown panic attacks, number of limited symptom attacks, percent time worrying, MC-PAS, CGI-Severity, CGI-Improvement, HAM-A, PGE, and Q-LES-Q (quality of life) ratings.

Preliminary Results: 398 subjects from 31 U.S. centers entered the study; at week 52, 183 subjects were randomized, 93 to sertraline, 90 to placebo. Less than 5% of subjects discontinued the study due to insufficient clinical response during 52 weeks of open-label treatment. Rates of discontinuation due to relapse or insufficient clinical response (12% in sertraline group vs. 24% in placebo group) and rates of acute exacerbation of Panic Disorder (13% in sertraline group vs. 30% in placebo group) were each statistically significant ($p<0.05$). Sertraline was statistically more effective than placebo as measured by change in the double-blind baseline to endpoint on percent time worrying, CGI-Serverity, CGI-Improvement, and PGE scores.

Conclusion: Sertraline was effective in long-term treatment in Panic Disorder for up to 80 weeks. Sertraline was substantially better than placebo in prevention of worsening of Panic Disorder symptoms.

Study Funded by Pfizer Inc.

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Poster No. 112

Long Term Safety of Paroxetine in Social Anxiety Disorder

David Carpenter, RPh, MS, Cornelius Pitts, RPh, Rosemary Oakes, MS, and Raj Kumar, MD

SmithKline Beecham Pharmaceuticals, 1250 S. Collegeville Rd., Collegeville, PA 19426

The efficacy and safety of paroxetine hydrochloride (PAXIL®), a Selective Serotonin Reuptake Inhibitor (SSRI), in social anxiety disorder (social phobia, 300.23, DSM-IV) were recently demonstrated in three acute (12-week), randomized, double-blind, placebo-controlled trials. The long-term safety, as well as long-term maintenance of effect, of paroxetine in this underdiagnosed and undertreated disorder were also assessed in an optional 40 week extension study for completers of one of the acute 12-week studies. In the extension study, patients received open-label paroxetine for 24 weeks with resulting responders then randomized to either double-blind continuation of paroxetine or to placebo substitution for another 16 weeks.

Given its well-documented safety during long-term use in patients with other mood/anxiety disorders (depression, OCD, panic disorder), paroxetine is expected to demonstrate similar safety during long-term use in patients with social anxiety disorder. This report descriptively compares the incidence of adverse experiences (AEs) during maintenance therapy with paroxetine (> 6 months) with the incidence of AEs occurring during acute administration in patients with social anxiety disorder.

The majority of the 578 total patients (62.3%) exposed to paroxetine during the social anxiety disorder clinical development program received paroxetine for a minimum of 3 months (i.e., double-blind plus open-label exposure), with approximately 10% (n=58) undergoing long term (>6 months) treatment. Ten patients received paroxetine for at least one year. In general, the mean maximum total daily dosage was similar between patients exposed to paroxetine for ≤ 6 months to those with exposure > 6 months (38mg/day).

There were very few AEs with a greater incidence during long-term exposure than during acute exposure. Those AEs that did exhibit a higher incidence with long-term exposure generally were reported in only 1-2 patients, were consistent with current adverse event labeling for other indications and rarely led to withdrawal from the study. In general, the incidence of those AEs which were commonly reported during acute treatment (i.e., ≥ 5% incidence and at least twice that of placebo) were lower following long-term therapy, suggesting that these commonly reported AEs may dissipate during chronic treatment. Thus, exposure of this patient population to paroxetine for a duration exceeding 6 months did not raise any new safety concerns that may be associated with the long-term use of this agent.

Because enrollment in the extension study was lower than projected, the study did not possess sufficient statistical power to detect a significant difference in the primary efficacy variable (the proportion of patients relapsing in the double-blind, placebo-controlled phase). A larger study to

assess the maintained efficacy (and safety) of paroxetine vs. placebo in the long term treatment of social anxiety disorder is underway.

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Poster No. 115

VALPROATE TREATMENT OF POST-TRAUMATIC STRESS DISORDER

Frederick Petty, Ph.D., M.D., Martin Kram, M.D., Lori L. Davis, M.D., Alexandria Nugent, M.eD., Michele Bollig. R.N., Virginia Gajewski, R.N., Gerald L. Kramer, B.A.

Veterans Affairs Medical Center, University of Texas Southwestern Medical Center, Dallas, Texas

Pharmacotherapy for post-traumatic stress disorder (PTSD) represents a relatively new treatment strategy for this potentially devastating mental illness. At this time, there are only about ten blinded, randomized, placebo controlled trials of drug therapy for PTSD. Valproate has been tested in PTSD in one open label study, with results that suggested efficacy for symptoms of anxiety and depression, but not for the "core" symptoms of intrusive thoughts. We have completed an open label study of valproate in thirty three males with chronic, treatment refractory, combat induced PTSD. Patients symptoms were measured weekly using Clinically Administered PTSD Scale (CAPS), and the Hamilton Ratings Scales for Anxiety and Depression (HAM-A and HAM-D). CAPS scores decreased significantly during the first four weeks of therapy with a significant decrease in the avoidance and hyperarousal subscales of the CAPS. Significant decreases in the Hamilton Rating Scales were also seen in most patients. The present study adds to a small but growing literature suggesting that pharmacological agents may be particularly useful in treatment of PTSD. Whether valproate is particularly efficacious in the pharmacotherapy of PTSD and is comparable to other treatment modalities awaits future blinded randomized studies. In summary, this open label study of valproate for chronic PTSD demonstrated positive results and justifies blinded, placebo-controlled clinical trials.

Poster No. 116

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Poster No. 117

Fluvoxamine in PTSD: Improvement in Physiological Reactivity to Trauma Cues

Phebe M. Tucker, M.D., Kurt L. Smith, M.A.[1], Brian Marx, Ph.D.[2], Dan E. Jones, PhD.[1], and Robert Miranda, M.S.[2]

[1]Department of Psychiatry and Behavioral Sciences, University of Oklahoma
WP 3440, P.O. Box 26901, Oklahoma City, OK 73190

[2]Oklahoma State University, Stillwater, Oklahoma

Background: Individuals with PTSD often have physiological arousal to reminders of trauma as well as intrusive re-experiencing symptoms, avoidance, and numbing. Physiologic reactivity to taped trauma scripts has been shown to reliably distinguish PTSD patients from controls in both veterans and civilians[1], and may be a useful indicator of response to pharmacologic and other treatments. Selective serotonin reuptake inhibitors have improved subjective PTSD symptoms in both controlled and uncontrolled trials[2]. The current study compares physiologic reactivity and subjective symptoms in PTSD patients and controls before and after treatment with fluvoxamine. Investigators attempt to determine if: 1) PTSD patients can be distinguished from traumatized controls in physiological reactivity to trauma scripts; 2) PTSD patients treated with fluvoxamine improve in subjective symptoms and autonomic reactivity; and 3) treated PTSD patients can be distinguished from controls in physiologic reactivity.

Methods: Sixteen patients with PTSD were compared at baseline to 16 mentally healthy, age- and gender-matched controls exposed to at least one serious trauma. Baseline psychometric ratings (CAPS) and physiological assessments of heart rate and blood pressure responses to individualized, taped trauma scripts were performed for subjects in both treatment groups. Colbourn and Kritikon Dinamap Vital Signs monitor (1846 SX) instruments were used. After the 16 PTSD patients received open-label fluvoxamine treatment (100-300 mg/day) for 10 weeks, psychometric and physiologic measures were repeated. Statistical analyses employed Pearson product-moment correlation coefficients (Dunn corrected), discriminant analysis, and paired t-tests.

Results: PTSD patients showed greater autonomic reactivity in heart rate, systolic and diastolic blood pressure and mean arterial pressure than controls at baseline. Discriminant analysis indicated that systolic blood pressure best classified PTSD patients (75% sensitivity) and controls (100% specificity), with stepwise discriminant analysis showing that combined physiological variables correctly classified 75% of PTSD subjects and 100% of controls. After 10 weeks of fluvoxamine treatment, self-report PTSD symptoms improved significantly, as did measures of heart rate, systolic and diastolic blood pressure reactivity. Also, PTSD patients could not be significantly distinguished from healthy controls in physiological reactivity to trauma cues after 10 weeks of fluvoxamine.

Significance: Fluvoxamine treatment of PTSD significantly improved subjective symptoms and autonomic reactivity such that treated PTSD patients resembled healthy controls in lack of reactivity to trauma cues. Thus, the current study demonstrates that physiologic assessment techniques are useful in substantiating subjective measures of improvement in PTSD treated with an SSRI, validating results of this open-label clinical trial.

References:

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Poster No. 118

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Poster No. 119

Abstract Title: Bupropion SR vs. Placebo in the Treatment of PTSD

Lori L. Davis, MD[1], Sandra Nevels, RN[2], Charles Nevels, MD[2], Jason Farley, RN[2], Cesar Munoz, MD[3], Al Bartolucci, PhD[3], Patricia Canales, PharmD[4], Fred Petty, PhD, MD[5]

[1]VA Medical Center, 3701 Loop Road East, Tuscaloosa, AL 35404

[2]VA Medical Center, Tuscaloosa, AL; [3]University of Alabama at Birmingham, Birmingham, AL; [4]Auburn University, Auburn, AL; [5]VA Medical Center, Dallas, TX

Background: Posttraumatic stress disorder (PTSD) is a serious, chronic mental illness that is often difficult to treat. The majority of research on the pharmacotherapy for PTSD has been focused on tricyclic antidepressants and serotonin reuptake inhibitors in small sample sizes. The results are mixed and especially poor in the veterans. Bupropion possesses a unique mechanism of action that is different from these previously tested medications. Bupropion decreases norepinephrine turnover, reduces the firing rate of noradrenergic neurons, and may have inhibitory effects on dopamine reuptake. These neurotransmitters have been implicated in the pathophysiology of PTSD. The current study evaluates the clinical efficacy and tolerability of bupropion sustained release in the treatment of PTSD.

Methods: After providing informed consent, 65 patients (95% veterans) with SCID confirmed PTSD who met inclusion and exclusion criteria were randomly assigned to bupropion SR versus placebo treatment in a double-blind fashion and followed for 8-weeks. Symptoms were rated with the Clinician Administered PTSD Scale (CAPS), Hamilton Rating Scale for Depression, Hamilton Rating Scale for Anxiety, and PTSD Checklist. Bupropion SR was initiated at 150mg/day and increased to 150mg twice daily on day 7. At week 4, and additional 100mg was added if needed. Response was defined as ≥ 50% decrease in CAPS.

Results: An interim blinded analysis of 50 patients with last observation carried forward shows a difference between group A versus B in change over time in CAPS (p=0.0992). The statistician has not been informed which treatment represents A or B (either placebo or active). The investigators have not been informed which patients are assigned to A or B. Enrollment has closed and the remaining 15 patients are completing the trial. Our power analysis indicates that 60 should be sufficient to show a significant difference between groups. Considering patients who completed at least week 4, there was a significant difference in response (≥ 50% decrease CAPS) on B (7/15=46.7%) vs. A (2/21=9.5%) using a Fisher Exact test (p=0.019). For patients completing the 8-week study, responders to B was 60% vs. 15.4% on A (p=0.039). These data have not been adjusted for multiple testing and could change with a full data set.

Significance: These data show promise for a new psychopharmacologic approach to the treatment of PTSD. This study is also the largest single site controlled pharmacologic trial in

PTSD to date. In addition, proven efficacy of a medication in a primarily veteran population would be very significant given the previous limited study in veterans.

Funding support: Glaxo Wellcome

Poster No. 120

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Poster No. 125

Pretreatment Anxiety Does Not Predict Response to Bupropion SR or Sertraline

A. John Rush, MD[1], Sharyn R. Batey, PharmD[2]; Rafe M. J. Donahue, PhD[2], John A. Ascher, MD[2], Tom Carmody, PhD[3]

[1]University of Texas Southwestern Medical Center at Dallas, Department of Psychiatry, 5323 Harry Hines Blvd., Dallas, TX 75235-9086
[2]Glaxo Wellcome Inc., Research Triangle Park, NC
[3]University of Texas Southwestern Medical Center at Dallas, Dallas, TX

Background

This analysis was undertaken to determine whether pretreatment (baseline) anxiety levels were predictive of antidepressant response to bupropion sustained release (bupropion SR), sertraline, or placebo in outpatients with recurrent major depression, and to determine whether bupropion SR or sertraline is preferred for use in patients with high pretreatment anxiety.

Methods

Retrospective *post hoc* analyses were conducted using pooled data from two identical, randomized, double-blind, placebo-controlled, acute phase studies that compared bupropion SR (150-400mg/day) and sertraline (50-200mg/day) to placebo in adult outpatients with recurrent major depression. Pretreatment anxiety was assessed by the 14-item Hamilton Rating Scale for Anxiety (HAMA). Antidepressant efficacy was measured by the 21-item Hamilton Rating Scale for Depression (HAMD-21). Response was defined as a drop in pretreatment HAMD-21 score of at least 50%. Analysis of covariance (ANCOVA) and logistic regression were used to examine the relationships between treatment and pretreatment HAMA scores.

Results

A total of 692 patients were randomized to bupropion SR (n=234), sertraline (n=225), and placebo (n=233). Pretreatment HAMA total scores were comparable between the three treatment groups (18.8 for bupropion SR, and 18.6 for both sertraline and placebo). Analyses showed that pretreatment anxiety was unrelated to response within the bupropion SR and within the sertraline treatment groups (p=0.43 and p=0.89, respectively). Patients were as likely to respond to either antidepressant independent of their level of pretreatment anxiety.

Conclusions

In patients with recurrent major depression, pretreatment anxiety did not predict preferential response to either bupropion SR or sertraline. These data indicate that the severity of a patient's pretreatment anxiety should not be used as a criterion in selecting between bupropion SR and sertraline.

The research described in this abstract was funded by Glaxo Wellcome Inc

Poster No. 126

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Poster No. 127

The Responsiveness of the Hamilton Depression Rating Scale

Douglas Faries, Ph.D.[1], John Herrera, Ph.D. [1], Jyoti Rayamajhi, Ph.D. [2], David Debrota, M.D.[1], Mark Demitrack, M.D.[1] , William Z Potter, M.D., Ph.D. [1]

[1] Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 [2] MedFocus, Des Plaines, IL

In clinical studies of antidepressants, the Hamilton Depression Rating Scale (HAMD) total score has been the gold standard instrument for establishing and comparing the efficacy of new treatments. However, the HAMD is a multidimensional measure, which may reduce its ability to detect difference between treatments, in particular, changes in core symptoms of depression. Two meta-analyses were conducted to compare the responsiveness of the HAMD total score with several published unidimensional subscale scores based upon core symptoms of depression. The first compared the above instrument's ability to detect differences between fluoxetine and placebo across 8 studies involving over 1600 patients. The second analysis involved 4 studies and over 1200 patients randomized to tricyclic antidepressants and placebo. In both meta-analyses, the unidimensional core subscales outperformed the HAMD total score at detecting treatment differences. The implications of this on sample sizes and power for clinical studies will be discussed. In fact, studies based on the observed effect sizes from the core subscales would require approximately 1/3 less patients than studies based on the HAMD total score. Effect sizes from each individual HAMD item will also be presented to help explain the differences in responsiveness between the scales.

Poster No. 128

An Open-Label Trial of St. John s Wort in Obsessive Compulsive Disorder

Leslie vH. Taylor, M.D., and Kenneth A. Kobak, Ph.D.

Dean Foundation for Health Research and Education, 2711 Allen Blvd, Middleton, WI 53562

Background: Recent interest in and evidence for the efficacy of St. John s Wort (hypericum perforatum) for the treatment of mild to moderate depression has led to speculation about it s efficacy in other disorders. Hypericum s mechanism of action is postulated to be via inhibition of the synaptosomal uptake of serotonin. As such, there is a suggestion that hypericum may be effective for obsessive compulsive disorder (OCD). While no open or controlled trials have been published, one case report found significant improvement with 300 mg of 3% hypericum twice daily (Currents in Affective Illness, 10/10/97).

Methods: Eight subjects were recruited with a primary DSM-IV diagnosis of OCD of at least 12 months duration. Subjects needed a minimum Y-BOCS score of 16 and a maximum HAMD score of 13 at baseline. Three of the subjects failed to respond to a previous trial of fluvoxamine. Treatment lasted for 12 weeks, with a fixed dose of 450 mg of 0.3% hypericin twice daily (extended release formulation). Weekly evaluations were conducted with the Y-BOCS, PGI, and CGI, and monthly evaluation with the HAMD. We report here results from the first 9 weeks of treatment (the study is ongoing).

Results: One patient discontinued after baseline due to rash (undocumented) and was lost to follow up. One other patient was lost to follow-up at week 6. Results are summarized below:

WEEK										
0	1	2	3	4	5	6	7	8	9	
Y-BOCS		19.57	16.00	14.71	15.29	15.33	15.43	14.17	11.66	12.66	12.33
change			3.57	4.85	4.29	4.5	4.14	5.00	7.50	6.50	6.83
p			.006	.006	.048	.051	.036	.085	.004	.019	.037

At week 9, 4 of 6 were rated much or very much improved on the CGI, 1 was minimally improved and 1 no change . Most common side effects reported were diarrhea (n=2) and restless sleep (n=2).

Conclusions: A significant change from baseline was found with Hypericum at 9 weeks, with a Y-BOCS drop similar to that found in clinical trials. The fact that a significant change was found as early as one week into treatment suggests a possible placebo response. Improvement grew larger over time. Results warrant larger open trials and/or a placebo controlled study of hypericum in OCD.

This research was supported by a grant from the OC Foundation. Alterra (hypericum perforatum) was donated by Upsher-Smith Laboratories Inc.

Poster No. 129

SIDE EFFECTS AND TIME COURSE OF RESPONSE IN A PLACEBO-CONTROLLED TRIAL OF FLUOXETINE IN GERIATRIC DEPRESSION

Deborah L. Ackerman, M.S., Ph.D.[1]; Sander Greenland, M.S., Dr.P.H.[1]; Alexander Bystritsky, M.D. [2]; Gary W. Small, M.D.[2,3,4]

[1]Department of Epidemiology, UCLA School of Public Health, Box 951772, Los Angeles, CA, 90095-1772
[2]Department of Psychiatry and Biobehavioral Sciences, UCLA Neuropsychiatric Institute, Los Angeles, CA

The often high placebo response rate can complicate the evaluation of true drug effect in controlled clinical trials. We reanalyzed data from a large, multicenter, placebo-controlled clinical trial of fluoxetine treatment of geriatric depression to evaluate similarities and differences between responders and nonresponders in both treatment groups. Fluoxetine was superior to placebo on all outcome measures, but response rates varied across sites. Clinical differences in the patient populations may have contributed to the different response rates.

We used Mantel-Haenszel tabular methods and multinomial (polytomous) logistic regression to examine (1) clinical differences among the 671 patients at the 30 sites, (2) side effects as possible predictors of response and of drop-out, and (3) the time course and onset of response.

We found that larger sites had higher response rates: Patients at larger sites tended to have less severe depression as measured by the CGI and the GDR, more severe depression as measured by the HAMD21, higher cognitive disturbance scores, and lower psychomotor retardation scores.

Among somatic complaints associated with fluoxetine response, headache before and after randomization was associated with good response; and constipation and anxiety after randomization were associated with poor response. Somnolence before and after randomization was associated with good placebo response.

Early and persistent improvement occurred among similar proportions of responders in both groups. The difference between fluoxetine and placebo appeared to be a persistent response beginning during the 4th week. Pretreatment somnolence was associated with early, persistent improvement in both groups, and may serve as a marker for placebo response.

Further evaluation of the common symptoms of depression, their interaction with the natural course of illness, and with drug treatment could determine whether these symptoms can be used by clinicians to guide treatment.

This work was supported by NIMH grant MH-53935.

Poster No. 130

Determination of SJW Differential Metabolism at CYP2D6 and CYP3A4, Using Dextromethorphan Probe Methodology

Benjamin Ereshefsky[1,3], Nevin Gewertz[1,3], Y.W. Francis Lam, Pharm.D. [1], Lidia M. Vega, B.S.[1], Larry Ereshefsky, Pharm.D. [1,2],

[1]Dept. of Pharmacology and [2]Dept. of Psychiatry University of Texas Health Science Center, 7703 Floyd Curl Dr. San Antonio, Tx 78284-6220 [3]Health Careers High School, San Antonio, Texas

St. John's Wort (SJW) is a commonly used over-the-counter herbal remedy for symptoms of mild depression. It contains a multitude of chemical compounds whose metabolic interactions have not been characterized. Since a number of antidepressants cause metabolic inhibition at cytochrome P450 (CYP) enzymes, we evaluate the potential of SJW to interact with drugs at CYP2D6 and CYP3A4.

We administer 30 mg of dextromethorphan (DM) cough syrup followed by a 6 hour urine collection. Using a validated HPLC assay with fluorescence detection, we determine the concentrations of DM and dextrorphan (DX) in urine; the DM/DX ratio characterizes and phenotypes subjects' metabolism at CYP2D6, with an antimode of 0.3 used to classify subjects into extensive or poor metabolizers (EM and PM). DM is also used as a probe for the CYP3A4 pathway, which transforms DM to 3-methoxymorphinan (3-Me); the urinary ratio of DM/3-Me characterizes metabolic capacity. In a previous study, we demonstrated the robustness of the simultaneous use of DM as a probe for both CYP2D6 and 3A4. Significant alterations in DM/3-Me ratios with the administration of grapefruit juice were observed while the DM/DX ratio remained unchanged (NCDEU 1998).

16 subjects, 14 EMs and 2 PMs, were studied to evaluate the effects of SJW on CYP2D6 and CYP3A4, by evaluating the change in the DM/DX and DM/3-Me urinary metabolic ratios from baseline. Each subject was coadministered DM and a 200 mg caffeine tablet to establish baseline metabolism. Caffeine administration is part of a larger study design, reported separately. This procedure was then repeated after 8 days of SJW dosing at 300 mg TID to insure steady-state conditions. No other medications or comorbid illnesses that might affect drug metabolism were allowed, and subjects abstained from alcohol, caffeine, and smoking.

The mean EM DM/DX ratios at baseline and following SJW administration were 0.009±0.013 vs. 0.007±0.004. There was no significant difference between the two mean urinary ratios for EMs (ANOVA, F=0.346, df=26, p=0.5617). The mean PM DM/DX ratios at baseline and following SJW were 2.626±0.176 versus 1.206±0.860. The mean DM/3-Me ratio for all patients (EM and PM) at baseline was 11.161±10.209 and the mean ratio post-SJW administration was 6.090±3.146. The DM/3-Me urinary metabolic ratio failed to achieve

significant changes from baseline (ANOVA F=3.605, df=1,30, p=0.0672), but trended towards increased metabolic capacity.

To place these negative findings into perspective, a metanalysis of the percent change from baseline for DM/DX for SJW subjects was compared with a similar population given four antidepressants in a study of nearly identical design; significant differences were found between treatments (ANOVA F=16.228, df=4, 52, p<0.0001). The potent CYP2D6 inhibitors fluoxetine (p<0.0001) and paroxetine (p<0.0001) demonstrated significantly greater percent changes in DM/DX from baseline than did SJW, mean percent changes were –3,310.314±3,419.51, –4,462.437±2,712.75, and –26.97±64.38, respectively. Sertraline (p=0.954) and venlafaxine (p=0.9888), drugs known for weak CYP2D6 inhibition, demonstrated no significant differences in their mean percent changes versus SJW, -58.74±75.10%, and –27.144±58.02%, respectively. The mean percent change from baseline in DM/3-Me in subjects receiving SJW was significantly lower than with grapefruit juice, -17.743% and –165.159%, respectively (ANOVA F=7.995, df=1, 25, p=0.0091).

The data presented demonstrates that SJW does not interact with CYP2D6 and CYP3A4. SJW's potential to interact at CYP2D6 is approximately the same as for venlafaxine or sertraline. Furthermore, SJW is a significantly weaker inhibitor of CYP3A4 then grapefruit juice. Additional studies utilizing a larger sample size is required to fully validate and confirm our findings.

Poster No. 131

Determination of the Differential Effects of St. John's Wort on the CYP1A2 and NAT2 Metabolic Pathways Using Caffeine Probe Methodology.

Nevin Gewertz[1,2], Benjamin Ereshefsky[1,2], Y. W. Francis Lam, Pharm.D. [1], Raymond Benavides, B.S.[1], and Larry Ereshefsky, Pharm.D. [1,3]

[1] Division of Pharmacotherapy, Departments of Pharmacology and Psychiatry, University of Texas Health Science Center, 7703 Floyd Curl Dr. San Antonio, TX 78284-6220

[2] Health Careers High School, San Antonio Texas

[3] Department of Psychiatry, University of Texas Health Science Center, 7703 Floyd Curl Dr. San Antonio, TX 78284-6220

St. John's Wort (SJW) is a commonly used herbal remedy for the treatment of symptoms of depression. There is little to no data available on the potential of SJW interactions with other medications. The use of validated probe drugs to characterize metabolic capacity and changes under varying conditions is possible. *In vivo* testing is particularly useful to evaluate complex remedies such as SJW where there are a myriad of chemical components and their metabolites.

Caffeine is an established *in vivo* probe that characterizes the metabolic capacity of the cytochrome P450 (CYP) 1A2 and N-acetyltransferase (NAT2) enzymes. Caffeine is converted into paraxanthine (17DMX), which is in turn converted to an unidentified compound called "Z" via CYP1A2. The plasma ratio of 17DMX/caffeine characterizes CYP1A2 metabolism. Furthermore, this "Z" compound is converted into three metabolites, AAMU, 1MU, and 1MX through the NAT2 metabolic pathway. The urinary ratio of AAMU/(1MU+1MX+AAMU) is used to simultaneously characterize NAT2 metabolism classifying patients as either fast or slow acetylators.

We evaluated SJW's effect on key metabolic enzymes by quantitating the changes *in vivo* of the metabolism of caffeine administered as a 200-mg tablet and 30 mg of dextromethorphan (DM). In this report, the effect of St. John's Wort on CYP1A2 and NAT2 metabolic pathways was determined as part of a larger study which also studied the effects of SJW on DM. Using a validated HPLC assay with fluorescence detection we measure the concentration of caffeine and its metabolites in order to calculate the caffeine metabolic ratios (CMRs) that can characterize and phenotype subject's metabolic capacity.

After caffeine probe administration, urine was collected for 6 hours after which 10ml of venous blood was drawn. 16 subjects were studied to evaluate their 17DMX/caffeine plasma ratio and their NAT2 CMR following caffeine administration. A baseline was established. Then,

after eight days, in which patient's took one 300mg tablet of SJW three times daily, caffeine and collection of urine and plasma for CMRs was repeated. The mean 17DMX/caffeine ratios were not significantly different (CYP1A2) at baseline versus following SJW; 0.325 ± 0.136 versus 0.365 ± 0.169, respectively (ANOVA, F=0.556, df=1, 30, p=0.4616). The mean CMRs were not significantly different (NAT2) at baseline versus following SJW; 0.299 ± 0.124 versus 0.282 ± 0.136, respectively (ANOVA, F=0.134, df=1, 30, p=0.7165). Although no genotyping was performed it appears that 5 of 16 subjects are slow acetylators based on a bimodal distribution in CMR: fast acetylator = 0.227±0.056 versus slow acetylator = 0.458±0.061 ($p<0.001$, F= 55.52, df=1,14) with a suggested "antimode" of 0.35. The mean CMR for the fast acetylators (previous sentence) did not demonstrate significant change from baseline versus SJW, CMR= 0.236±0.118 (p=0.819, F=0.053, df= 1,20). Slow acetylator status patients were excluded since they are unlikely to demonstrate a potential drug interaction effect at NAT2.

This preliminary study presents data supporting a low potential for SJW drug interactions at CYP1A2 and NAT2 metabolic pathways. Furthermore, the utility of probe methodology to simultaneously determine several metabolic pathways was demonstrated. Further study is required with a larger sample size to validate these findings.

Poster No. 132

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Poster No. 133

Contribution of the Menstrual Cycle to Instability of Depressive Severity

Annie Harvey, Ph.D., Psychiatric Research Institute, 1100 N. St. Francis, Wichita, KS 67214-2878

Introduction Women are twice as likely as men to suffer from major depressive disorder and onset is highest during the reproductive years. Menstrual cycle phase can predict the presence of depressive symptoms in otherwise asymptomatic women. Yet, the effect of the menstrual cycle on symptom severity in currently depressed women is not well described. Data from ongoing clinical trials were used to test the hypothesis that the menstrual cycle makes a major contribution to instability of depressive severity in depressed women.

Methods The 17-item Hamilton Depression (HAM-D) scores at each visit were examined over the course of three clinical trials of depressed outpatients (72 women, 30 men). An instability score was constructed based upon the difference between the HAM-D score observed at a visit, and that predicted by averaging HAM-D scores of the preceding and succeeding visits. This measure was used to describe that visit's instability. Next, instability was averaged over all a patient's visits and weighted to emphasize punctate instability as opposed to a chronic pattern of unstable depressive severity such as might be associated with personality disorder. This measure was used to describe the patient's overall instability. Patient records were examined to determine the sex and ovarian status (naturally cycling or not) of each patient, whether a change in rater had occurred at any visit, and what life events had been reported at each visit. The potential contribution of the menstrual cycle to instability was compared to the contribution of a change in raters and that of reported life events.

Results At nearly 70% of all visits instability was low, i.e. the HAM-D deviated from predicted by no more than 3 points. At 11% of visits HAM-D scores deviated by at least 6 points. Change in raters and reported life events made insignificant contributions to visit instability.

Overall instability exceeding an empirically derived threshold, above which instability was considered clinically significant, was used to define "unstable" patients. Cycling women (n = 53) were disproportionately unstable ($p = .0062$, Fisher's exact test), and nearly one quarter of them could be so described. In the single study capturing dates of menses there was a large effect of cycle phase. Among the 12 spontaneously menstruating women participating in that study instability was significantly greater ($p < .05$) in the 4 days prior to menses than it was midcycle (day 9 through day -13 of a standardized 28-day cycle).

Conclusions Menstrual cycle phase makes a substantial contribution to instability of depressive severity. The clinical and pathophysiological implications merit further study.

This work was sponsored by the Psychiatric Research Institute.

Poster No. 134

SIDE EFFECTS AND TIME COURSE OF RESPONSE IN A PLACEBO-CONTROLLED TRIAL OF FLUOXETINE IN GERIATRIC DEPRESSION

Deborah L. Ackerman, M.S., Ph.D.[1]; Sander Greenland, M.S., Dr.P.H.[1]; Alexander Bystritsky, M.D. [2]; Gary W. Small, M.D.[2,3,4]

[1]Department of Epidemiology, UCLA School of Public Health, Box 951772, Los Angeles, CA, 90095-1772
[2]Department of Psychiatry and Biobehavioral Sciences, UCLA Neuropsychiatric Institute, Los Angeles, CA

The often high placebo response rate can complicate the evaluation of true drug effect in controlled clinical trials. We reanalyzed data from a large, multicenter, placebo-controlled clinical trial of fluoxetine treatment of geriatric depression to evaluate similarities and differences between responders and nonresponders in both treatment groups. Fluoxetine was superior to placebo on all outcome measures, but response rates varied across sites. Clinical differences in the patient populations may have contributed to the different response rates.

We used Mantel-Haenszel tabular methods and multinomial (polytomous) logistic regression to examine (1) clinical differences among the 671 patients at the 30 sites, (2) side effects as possible predictors of response and of drop-out, and (3) the time course and onset of response.

We found that larger sites had higher response rates: Patients at larger sites tended to have less severe depression as measured by the CGI and the GDR, more severe depression as measured by the HAMD21, higher cognitive disturbance scores, and lower psychomotor retardation scores.

Among somatic complaints associated with fluoxetine response, headache before and after randomization was associated with good response; and constipation and anxiety after randomization were associated with poor response. Somnolence before and after randomization was associated with good placebo response.

Early and persistent improvement occurred among similar proportions of responders in both groups. The difference between fluoxetine and placebo appeared to be a persistent response beginning during the 4th week. Pretreatment somnolence was associated with early, persistent improvement in both groups, and may serve as a marker for placebo response.

Further evaluation of the common symptoms of depression, their interaction with the natural course of illness, and with drug treatment could determine whether these symptoms can be used by clinicians to guide treatment.

This work was supported by NIMH grant MH-53935.

Poster No. 135

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Poster No. 136

Differential Affective Symptom Response During GnRH Agonist Therapy for Endometriosis

David W. Morris, M.A.[1], Julia K. Warnock, M.D., Ph.D.[2] and J. Clark Bundren, M.D.[3]

[1]The University of Tulsa, Department of Psychology, 600 South College Avenue, Tulsa, OK, 74104-3189
[2]University of Oklahoma Health Sciences Center-Tulsa, Department of Psychiatry, Tulsa, OK,
[3]University of Oklahoma Health Sciences Center-Tulsa, Department of Obstetrics and Gynecology, Tulsa, OK

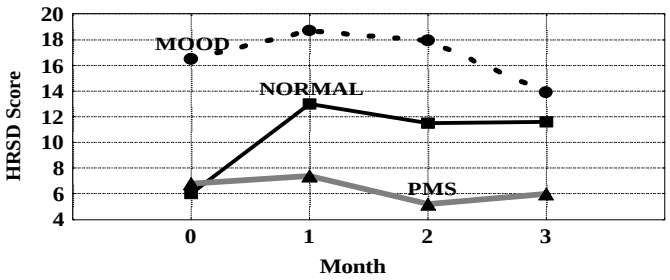
BACKGROUND: Studies of the psychiatric uses, as well as the side effects associated with GnRH agonist have yielded inconsistent findings. The authors believe some of these inconsistencies may be due to the combination of patients with a wide range of affective vulnerability into study groups. Specifically, women with a current vulnerability to affective dysregulation may have been combined with normals as well as subjects with Premenstrual Dysphoric Disorder (PDD). Based upon a brief pretreatment psychiatric assessment patients can be assigned to one of three groups, each with a unique subsequent affective response to GnRH agonist therapy.

METHODS: Thirty-one women with laproscopically diagnosed endometriosis who presented for treatment at a university affiliated infertility clinic were evaluated prior to receiving luprolide acetate therapy (depot, 3.75 mg IM every 28 days). Patients were assessed monthly using a Hamilton Rating Scale for Depression (HRSD) as well as standard lab (estradiol levels, height, weight, BP, etc.). After being screened for common Axis I disorders using the PRIME-MD, patients were assigned to one of three study groups. Group 1 (Mood) contained 11 women ranging in age from 22 to 46 (mean $\pm$ SD, 29.4 $\pm$ 7.9) with HRSD $\geq$ 10. Group 2 (Normal) contained 14 women ranging in age from 21 to 40 (29.8 $\pm$ 5.9) with HRSD < 10, and not qualifying for a DSM-IV diagnosis of PDD. Group 3 (PMS) contained 6 women ranging in age from 19 to 38 (30.0 $\pm$ 6.3) with HRSD < 10, and a current diagnosis of PDD.

RESULTS: An analysis of variance indicated statistically significant ($p<0.05$) between groups differences in HRSD scores from month 1 to month 3 (the affective symptom response phase) , $F(2,18)=8.56$; $p<0.003$. A post hoc analysis (Newman-Keuls test) indicated statistically significant differences between each of the study groups across time. No statistically significant within group differences in HRSD scores were found across time (month 1 to 3). Patients in all three study groups dropped from normal estradiol levels to >20.0 pg/ml by month one. Note, by month 4, three subject in the Mood group were removed from the study and treated for depressive mood symptoms, perhaps explaining the decline in HRSD scores in the latter portion of the affective symptom response phase (see Figure 1).

CONCLUSIONS: Patients presenting for the medical treatment of endometriosis with GnRH agonists can be divided into three subgroups. It appears that each of the three groups (Mood, Normal, PMS) have a unique affective symptom response. Thus, clinicians may expect patients with PDD will have minimal depressive symptoms; patients with affective symptoms at the onset of GnRH agonist therapy will continue to experience significant affective symptoms. Women with normal mood at the initiation of

Figure 1
Hamilton Rating Scale for Depression (HRSD)



luprolide treatment will have an increase in affective symptoms.

Poster No. 137

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Poster No. 138

Pramipexole in the Treatment of Markedly Depressed Outpatients. Peter D. Londborg, M.D., Vincent Glaudin, Ph.D., and John R. Painter, Ph.D. Summit Research Network, 901 Boren Ave., Suite 1800, Seattle WA 98104

Introduction: Pramipexole, a full agonist for the dopamine D2 receptor, has been studied primarily in the treatment of Parkinson's disease and restless leg syndrome. **Purpose**: To evaluate the efficacy, tolerability and dosage of pramipexole in the treatment of major depression. **Design**: Double-blind, placebo-controlled, parallel groups randomized to one of 3 fixed doses of pramipexole (1mg, 3mg, or 7mg) or placebo for 8 weeks, with a post-study taper of 2 weeks. **Dosing**: Pramipexole 0.25mg twice a day was titrated to the fixed dose level over a period of up to 2 weeks. Dose reduction of 0.5mg was permitted per intolerance for the 1mg group; reduction of 1mg was permitted for the 3mg and 7mg patients. **Subjects**: Adult outpatients from Seattle (USA) who met DSMIII-R criteria for major depression were selected if total score on the Hamilton Rating Scale for Depression ($HRSD_{17}$) was at least 22 and depressed mood was rated at least 3 (item #1). **Measures**: Efficacy was assessed by mean change in $HRSD_{17}$ from baseline, by the Clinical Global Rating of Improvement (CGI-I) of at least much improved and by change in the Core Depression Cluster ($HRSD_{17}$ items 1,2,3 &7). Adverse events (AEs) were elicited at each visit, recorded in text, and converted to standard language. **Results**: *Efficacy*. 32 patients randomly assigned to each of 4 treatment conditions (n=9,8,8,&7 for placebo, 1mg, 3mg, and 7mg groups respectively) comprised the efficacy sample; 62% (20/32) completed 8 weeks of treatment. The 18 females and 14 males in the efficacy sample averaged 38 years of age; no significant differences among treatment groups for these demographic variables was found, nor were any significant differences observed in severity of depression at baseline. Mean $HRSD_{17}$ scores ranged from 23.1 to 25.1 and CGI-Severity from 4.75 to 5.25 at baseline. Repeated-measures ANOVA for $HRSD_{17}$ was significant for treatment group ($F=3.18$, $df=3$, $p<.039$) and approached significance for interaction between treatment and visit ($F=1.63$; $df=18$, $p<.057$). Pramipexole was significantly superior to placebo for the proportion of patients at least much improved at endpoint (Pearson $\chi^2 = 10.7$, $df=3$, $p<.013$); the greatest disparity was 75% (6/8) versus 0% (0/9) for 3mg and placebo respectively. Core depression (low mood and loss of interest) was significantly more improved for patients treated with pramipexole as assessed by repeated-measures ANOVA (main effect of group, $F=3.50$, $df=3$, $p<.028$; treatment by visit interaction $F=2.12$, $df=18$, $p<.007$). *Safety*. No serious AEs were recorded, but 48% (11/23) of patients were intolerant of pramipexole as the dose increased such that 71% (5/7) were intolerant of 7mg. Almost all patients (10/11) on active drug who dropped from treatment did so because of AEs, all associated with nausea. **Conclusions**: Pramipexole was demonstrated to be effective in the therapy of major depression of marked severity but its promise appears limited by intolerance (nausea). Further study is definitely warranted, especially in 2 and 3mg doses, because of its potential in treating severe and/or treatment-resistant depression. This potential is highlighted by impressive results in decreasing core symptoms of depression.

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Poster No. 143

Bupropion SR in Dysthmic Disorder

David Hellerstein, M.D.[1], Sarai Batchelder, Ph.D. [1], David Kreditor, M.D., Ph.D. [1] and Michael Fedak, M.D.[1]

[1] Beth Israel Medical Center, Department of Psychiatry, 1st Avenue at 16th street, New York, N.Y., 10003

Background: Treatment of dysthymia with SSRI medications has been extensively studied and has become widespread psychiatric practice in the United States. However, there is an absence of clinical trials of bupropion in this population. Since treatment of dysthymia often requires long-term continuation of medication treatment, we believe that bupropion SR's high tolerability and unique side effect profile makes it a particularly effective treatment of dysthymia. In particular, we believe that the low occurrence of weight gain and sexual dysfunction, common causes of treatment discontinuation, will result in increased compliance with treatment in this population of patients. The purpose of this 8-week, open-label study was to provide preliminary data on the tolerability and effectiveness of bupropion for patients with dysthymic disorder, as well as to explore this hypothesis regarding specific side effects. **Method:** To date, eleven subjects meeting DSM-IV criteria for dysthymic disorder have been enrolled. Dosing was initiated at 150 mg qAM and increased to a maximum of 200 mg BID if tolerated and clinically indicated. All eleven subjects completed the trial, a 0% drop-out rate. Thus the ITT and completer analyses are identical. **Results:** Of these 11 subjects, 7 (63%) were treatment responders. Paired sample t-tests were highly significant, indicating that, on average, there was significant improvement on all measures of symptomatology and functioning, with M$\pm$SD scores on the HamD decreasing from 21.36$\pm$6.45 at baseline to 6.27$\pm$3.52 at Week 8. The average dose at Week 8 was 355 mg/day (sd=85.01). Side effects were reported by 3 subjects and included headaches (n=2), decreases in libido (n=1), decreases in appetite (n=1), insomnia (n=2), palpitations (n=1), and gastrointestinal problems (n=1)**.** None of these side effects resulted in discontinuation of treatment. **Conclusion:** These findings provide preliminary evidence for the benefit of bupropion SR in the treatment of dysthymic disorder.

This study was supported by a research grant from GlaxoWellcome.

Poster No. 144

Bupropion SR vs Placebo in SAD: Controlled Trial

Danielle Webster R.N., C.S., M.S.[1]; Martin H. Teicher M.D., Ph.D[1,2]; Carol A. Glod R.N., C.S., Ph.D.[1,3]; Cynthia E. McGreeney[1]

Address: [1]Developmental Psychiatry Research Program, McLean Hospital 115 Mill St. Belmont , MA 02178; [2]Department of Psychiatry, Harvard Medical School, Boston MA; [3]School of Nursing, Northeastern University, Boston MA.

Objective: To ascertain efficacy of bupropion HCl in major depression with fall/winter seasonal pattern.

Method: Randomized double-blind placebo-controlled study of adults meeting DSM-IV and Rosenthal-NIMH criteria with titration to maximum daily divided dose of 400 mg over six week treatment period. Primary measures were structured Hamilton Depression Scale modified for SAD (SIGH-SAD) and Kellner's Symptom Questionnaire (SQ).

Results: To date, 46 subjects have entered the study, 8 are still enrolled, 7 have dropped out, and 31 have completed the protocol. Of the dropouts, 3 terminated prior to assignment of drug or placebo, 2 dropped out on medication and 2 dropped out from the placebo group during the first week of treatment.

Interim analysis of 31 subjects completing protocol during the first year and second year (13 meds/ 18 placebo) revealed efficacy of Bupropion SR over placebo. The greatest drug/placebo difference occurred in self-report rating of friendliness (a wellness factor on the SQ) which showed robust treatment by week interaction ($F[6,174] = 2.51$, $p = 0.02$). At end point, friendliness scores were up 2.2 points on drug (76% improvement) versus 0.55 points on placebo (16% improvement; $p < 0.02$). Total depression scores improved 59% on placebo vs. 79% on bupropion.

In this interim analysis there may be emerging evidence for gender difference in degree of placebo response. Women showed very little drug/placebo difference in degree of improvement in total depression scores (68% improvement on placebo vs. 76% improvement on medication; n=11,6 respectively). Men however, appeared to have a numerically greater differential response to drug (49% improvement on placebo vs 80% improvement on medication; n= 7,7 respectively). Comparable differences were also noted in degree of improvement in friendliness scores.

Discussion: Results suggest that Bupropion SR may be effective in treatment of SAD, and support Kellner's finding that the SQ is remarkably sensitive to drug effects on mood. Gender differences in placebo response may have implications for design of other studies of patients with recurrent seasonal depressions.

Supported, in part, by Glaxo Wellcome, Inc.

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Poster No. 147

MANAGEMENT OF DEPRESSION REFRACTORY TO SSRI TREATMENT: A SURVEY OF CLINICIANS

David Mischoulon, MD, PhD, Andrew A Nierenberg, MD, Leena Kizilbash, MD, Jerrold F Rosenbaum, MD, and Maurizio Fava, MD

Massachusetts General Hospital, Depression Clinical and Research Program, WAC-812, 15 Parkman Street, Boston, MA 02114

Objective: To examine treatment practices among physicians in cases where SSRIs are ineffective.

Methods: We surveyed 801 clinicians (including 630 psychiatrists, 38 physicians in other specialties, and various other practitioners) attending the Massachusetts General Hospital's annual psychopharmacology review course. Clinicians received a vignette about a depressed patient who had failed treatment with an SSRI, and were asked about their preferences among various strategies available to manage this patient.

Results: 466 clinicians (58%) returned the questionnaires. Clinicians who responded had been in practice a mean of 16.6 years (SD 10.7). 84% of clinicians chose to increase the dose of the SSRI; 10% of clinicians chose augmentation or combination; and 7% of clinicians opted for switching agents. Bupropion was the most widely chosen augmenting agent (30%), followed by Lithium (22%). When asked to switch to another agent, 52% of clinicians chose a newer antidepressant, 34% chose another SSRI, 10% chose a TCA, 2% chose an SNRI, 1% chose an MAOI, and 1% chose an undefined 'other' agent.

Conclusions: Clinicians in this sample preferred increasing the dose of the SSRI as the first-line strategy for treatment of refractory depression. Newer antidepressants were favored as second-line agents, and bupropion was the preferred augmenting agent.

Poster No. 148

Annual Health Care Expenditures and Compliance with Antidepressant Treatment in an MCO

James M. Russell, M.D.,[1] Andrew M. Baker, M.P.A.,[2] Amy N. Grudzinski, Pharm.D.,[2] and Salvatore V. Colucci, M.S,[3]

[1] The University of Texas Medical Branch at Galveston, 404 University Boulevard, Rebecca Sealy Suite 4.510, Galveston TX 77555-0191
[2] Pfizer, Inc., New York NY
[3] IPR Data Solutions LLC, Norwalk CT

Introduction: Treatment failure in individuals with depression due to poor compliance may increase health care costs by increasing outpatient visits and hospital admissions (Thompson et al., 1996). Therefore, treating depression with an antidepressant that increases compliance may lower overall medical costs.

Objective: To assess whether compliance with SSRIs is higher than TCAs and atypical/heterocyclic antidepressants, and if improved compliance reduces health care costs.

Methods: 1994-96 claims data from a large managed care organization (MCO) in the Southwestern US were used to identify patients diagnosed with a depressive disorder who began treatment with an SSRI, TCA, or atypical/heterocyclic antidepressant. Treatment duration, non-depression-related medical costs, and total health care costs by drug class and AHCPR compliance category were examined during the subsequent twelve-month period.

Results: Depressed patients prescribed SSRIs were more likely to be treated in accordance with AHCPR treatment duration guidelines (61% ≥ 150 days; $p<0.001$) and had lower non-depression-related medical costs ($p < 0.001$). Increased treatment duration with SSRIs but not TCAs or atypicals was associated with lower non-depression-related medical expenditures ($p = 0.039$ for 1Rx vs. ≥ 150 days). In patients treated in accordance with AHCPR treatment duration guidelines, total annual health care costs were lower for patients treated with SSRIs than for patients treated with atypical antidepressants ($p = 0.031$) and comparable to that of patients treated with TCAs ($p = 0.481$).

Conclusions: Total health care costs were lowest in SSRI treated patients. Non-depression-related costs were lowest in SSRI treated patients and these costs declined as compliance improved.

Supported by an unrestricted grant from Pfizer, Inc.

Poster No. 149

Efficacy and Tolerability of Quetiapine Compared with Haloperidol in Schizophrenic Patients Partially Responsive to Conventional Antipsychotic Treatment

Jeffrey Goldstein, Ph.D[1], Robin Emsley, M.D.,[2] Joher Raniwalla, BSc, B.M.,[3] Peter Bailey, BSc,[3]
and Martin Jones, BSc, MSc[3]
[1]Zeneca Pharmaceuticals, 1800 Concord Pike, PO Box 15437, Wilmington, DE 19850-5437
[2]Department of Psychiatry, Capetown, South Africa
[3]Zeneca Pharmaceuticals, Alderley Park, Macclesfield, UK

Most schizophrenic patients that practicing psychiatrists will treat are those who have not completely recovered from acute episodes, retaining clinically significant positive and negative symptoms. These patients may be referred to as partial responders. Quetiapine fumarate (quetiapine, SEROQUEL®), a novel atypical antipsychotic, is effective for treating schizophrenia and is well tolerated. This study compared the efficacy and tolerability of quetiapine with haloperidol in patients who did not experience a sufficient response to 1 month's treatment with fluphenazine. Schizophrenic patients with a history of persistent positive symptoms while previously taking antipsychotics were entered into the run-in phase of an international, multicenter, double-blind, randomized trial. In the run-in phase, all 365 patients received fluphenazine (20 mg/day) for 4 weeks. At the end of this period (Week 4, baseline) those patients showing a reduction in PANSS total score of <30% and a PANSS positive score of ≥ 15 (ie partial responders, n=288) were randomised to quetiapine (600 mg/day, n=143) or haloperidol (20 mg/day, n=145) for 8 weeks. Both quetiapine and haloperidol were associated with marked reductions in PANSS total scores (primary end point), the mean change from baseline after 4 and 8 weeks of treatment being greater for quetiapine (-9.05 & -11.50) than haloperidol (-5.82 & -8.87); the difference between treatments after 4 weeks of treatment approached statistical significance (-3.24, p=0.061). Statistically significantly more patients responded to treatment (defined a priori as ≥ 20% reduction in PANSS total score) in the quetiapine than the haloperidol group (52.2 vs 38.0%, p=0.043). All other secondary efficacy end points showed greater improvements with quetiapine than haloperidol (not statistically significant). Quetiapine was significantly better tolerated than haloperidol: fewer quetiapine patients required anticholinergics (44.3 vs 59.6%, p=0.011), had an increase in Simpson Scale score (23.9 vs 39.1%, p=0.005), experienced EPS-related adverse events (13.6 vs 30.5%, p<0.001). Fluphenazine elevated plasma prolactin, this was significantly reduced in the quetiapine compared with the haloperidol group (-601.39 vs -20.54 mU/ml, p≤ 0.001). Quetiapine would appear to be more effective, and better tolerated, than haloperidol in patients classed as partial responders.

Supported by a grant from Zeneca Pharmaceuticals

Poster No. 150

Atypical Antipsychotics: Longitudinal Changes in Inpatient Use

Stephen Saklad, Pharm.D.[1], Larry Ereshefsky, Pharm.D.[1], Dennis Pabis, Pharm.D.[1], Daniel Still, Pharm.D.[1], Julia Vertrees, Pharm.D.[1]

[1]Psychiatric Pharmacy Program, College of Pharmacy, The University of Texas, and San Antonio State Hospital. UTHSCSA, Dept of Pharmacotherapy, MCD 3.4, 7703 Floyd Curl Drive, San Antonio, TX 78284-6220

Background - Clozapine has revolutionized the care of the psychotic patient since its introduction as the first atypical antipsychotic. Analyses of the minimally restricted clinical use of these agents in a broad inpatient population allows the detection of useful insights into the pharmacotherapeutic differences in these agents outside of a well-controlled study population. These new antipsychotics have a much richer and more differentiated pharmacology than the original group of essentially similar dopamine receptor blockers. This differentiation allows more selective and effective use of these agents in routine clinical practice as well as identifying additional areas for prospective research.

Method - A detailed Retrospective Longitudinal Drug Use Review (RLDUR) of the pharmacy distribution records from 1995 to 1998 at a large state hospital was performed. The rate of use, dose and titration rate, duration of use, costs, concomitant medications, and duration of inpatient admissions and outpatient care were analyzed.

Results - Records for 27,900 treatment episodes were included for the 1134 patients (58% male) that received an atypical antipsychotic during 2370 inpatient stays. Pre/post-analysis of inpatient care duration since 1997 showed a significant difference between risperidone (N = 168, -0.154 ± 0.349) and olanzapine (N = 230, -0.235 ± 0.369): $F = 4.886$, $df = 1, 396$, $p = 0.0277$, Power = 0.590. Risperidone showed less of an increase in inpatient care than olanzapine. Diagnosis, age, ethnicity, gender, and length of inpatient care all appear to be significant covariates that reveal significant differences in outcome between agents.

Significance -The use pattern has shown changes suggesting that the clinical experience in a real world setting reveal important differences between these agents. The use of patient characteristics to guide selection of the optimal atypical antipsychotic may improve patient response and decrease the cost and duration of inpatient care for the psychotic patient.

This study was supported in part by an unrestricted educational grant from Janssen Pharmaceuticals to the Psychiatric Pharmacy Program of the University of Texas.

Poster No. 152

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Poster No. 156

The Link between Drug Attitudes, Compliance Behaviors, and Resource Use among Individuals with Schizophrenia

A. George Awad, M.D.,[1] Vera Mastey M.S.,[2]

[1] University of Toronto, Centre for Addiction and Mental Health, 250 College Street, Toronto, Ontario, Canada, M5T 1R8
[2] Pfizer Pharmaceuticals Group, New York, USA

This study was undertaken to assesses the link between compliance attitudes, behaviors, and resource use.
Cross-sectional data from a June 1998 survey of 354 individuals with schizophrenia was used in this study. Using the Drug Attitude Inventory (DAI), compliant attitudes are categorized as "non-compliant" (-10 to 0), "somewhat compliant" (1 to 6), and "very compliant" (7 to 10). Behaviors include medication switching (yes/no) and skipping (a 5-point scale).

More respondents with non-compliant attitudes switched their anti-psychotic medication in the past year (41%) than those who are somewhat (28%) or very (21%) compliant (P=.02). They are also more likely to report skipping medication ($p<.06$, ANCOVA, side effects controlled).

Respondents who switched their medications in the past year are more likely to have been hospitalized in the past six months (32%) than those who did not switch (12%) ($P<.001$). More switchers (32%) than non-switchers (20%) also report ER visits ($p<.03$). Those who skip their medications are more likely to have used the ER (38%) than those who did not skip (20%) (P=.02).

Clinicians need to assess and address patients' subjective feelings on medication and their attitudes towards them. Such factors can influence their compliance behavior as well as the extent of resource utilization.

Poster No. 157

Olanzapine vs. Clozapine: An International Double-Blind Study in the Treatment of Resistant Schizophrenia

Jean-Noël Beuzen, MD., Martin A. Birkett, MS., Gerilyn M. Kiesler, PharmD., Gary D. Tollefson, MD., PhD., Andrew J. Wood, PhD., Charles M. Beasley Jr., MD., and The Lilly Resistant Schizophrenia Study Group
Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285

Olanzapine (mean: 22.2 $\pm$ 3.9 mg/day) was compared to clozapine (mean: 354.2 $\pm$ 146.1 mg/day) in the treatment of patients with treatment resistant DSM-IV schizophrenia with $BPRS_{1-7}$ total score $\geq$ 45 and a score of $\geq$ 4 on at least 2 positive symptom psychosis items. Treatment resistance was defined as retrospective failure to respond adequately to 2 previous antipsychotic treatments, each from a different chemical class, given for at least 6 weeks at a dose of at least 500 mg chlorpromazine equivalents or highest tolerated dose. There were 90 patients treated with each agent in a double-blind randomized fashion for up to 18 weeks.

Mean change (LOCF) in PANSS scores were: Total (olanzapine -25.6, clozapine -22.1); Positive (olanzapine -6.8, clozapine -6.4); Negative (olanzapine -7.1, clozapine -5.6). Based on the PANSS Total Score, the treatment effect favored olanzapine by 3.5 points with a one-sided lower 95% confidence limit of -2.2 points. A lower limit of -4 points for the treatment effect was defined *a priori* as the basis of declaring "non-inferiority" and since the one-sided lower 95% confidence limit was $\geq$ -4, olanzapine was shown to be "non-inferior" to clozapine.

There were six spontaneously reported adverse events that occurred with significantly different incidences between the two treatments. Dry mouth was more frequent among olanzapine-treated patients. Constipation, increased salivation, dizziness, nausea, and tooth disorder were more common among clozapine treated patients. Treatment-emergent akathisia, arkinsonism, and dyskinesias occurred at comparable incidence as assessed by the Barnes Akathisia Scale, Simpson-Angus Scale, and AIMS.

Poster No. 158

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Poster No. 159

ECT in Clozapine Resistant Schizophrenia

Georgios Petrides, M.D.[1], Alan Mendelowitz, M.D.[1], Sorina Simion-Rodgers, M.D.[1], Max Fink, M.D.[1], Nina Schooler, Ph.D.[1]

[1] Psychiatry Research Department, Hillside Hospital, a division of North Shore-Long Island Jewish Health System, Glen Oaks, NY 11004

In a prospective open study, we augmented clozapine with electroconvulsive therapy (ECT). We included patients with clozapine-resistant schizophrenia as defined by the following criteria: a) DSM-IV diagnosis of schizophrenia, b) duration of illness of at least 2 years, c) clozapine treatment for at least 12 weeks and serum level >350 ng/ml, d) a score of at least four (moderate) in one of the psychosis items (hallucinatory, behavior, suspiciousness, disorganization, unusual thought content) of the Brief Psychiatric Rating Scale (BPRS) or 12 in these items combined, and e) a CGI of at least four (moderate). ECT was given with bilateral electrode placement 2-3 times per week for up to 8 weeks or 20 treatments. Patients were rated with BPRS weekly.

We treated four patients to date. All patients were male, between 25 and 32 years of age. The duration of their illness ranged from 8 to 14 years. The length of clozapine treatment prior to the augmentation with ECT was 12 weeks to 5 years. Clozapine dose ranged from 450 to 500 mg/d with serum levels between 370 and 775 ng/ml.

All patients improved and met the *a priori* criteria for response to the combined treatment: a reduction of 40% in the four psychosis items of BPRS. More specifically, Patient A showed a reduction of his symptoms, as rated by the four items of BPRS, from 18 to 7 (61%) after eight weeks. Patient B showed a reduction from 17 to 9 (48%) after five weeks, Patient C from 21 to 11 (48%) after two weeks, and Patient D from 17 to 10 (41%) after three weeks.

All patients tolerated the combined treatment well. We did not observe prolonged or spontaneous seizures nor other side effects besides the expected cognitive effects of ECT.

Further clinical data will be presented.

Poster No. 160

Efficacy and Tolerability of Quetiapine Compared with Haloperidol in Schizophrenic Patients Partially Responsive to Conventional Antipsychotic Treatment

Jeffrey Goldstein, Ph.D[1], Robin Emsley, M.D.,[2] Joher Raniwalla, BSc, B.M.,[3] Peter Bailey, BSc,[3]
and Martin Jones, BSc, MSc[3]

[1]Zeneca Pharmaceuticals, 1800 Concord Pike, PO Box 15437, Wilmington, DE 19850-5437
[2]Department of Psychiatry, Capetown, South Africa
[3]Zeneca Pharmaceuticals, Alderley Park, Macclesfield, UK

Most schizophrenic patients that practicing psychiatrists will treat are those who have not completely recovered from acute episodes, retaining clinically significant positive and negative symptoms. These patients may be referred to as partial responders. Quetiapine fumarate (quetiapine, SEROQUEL®), a novel atypical antipsychotic, is effective for treating schizophrenia and is well tolerated. This study compared the efficacy and tolerability of quetiapine with haloperidol in patients who did not experience a sufficient response to 1 month's treatment with fluphenazine. Schizophrenic patients with a history of persistent positive symptoms while previously taking antipsychotics were entered into the run-in phase of an international, multicenter, double-blind, randomized trial. In the run-in phase, all 365 patients received fluphenazine (20 mg/day) for 4 weeks. At the end of this period (Week 4, baseline) those patients showing a reduction in PANSS total score of <30% and a PANSS positive score of ≥ 15 (ie partial responders, n=288) were randomised to quetiapine (600 mg/day, n=143) or haloperidol (20 mg/day, n=145) for 8 weeks. Both quetiapine and haloperidol were associated with marked reductions in PANSS total scores (primary end point), the mean change from baseline after 4 and 8 weeks of treatment being greater for quetiapine (-9.05 & -11.50) than haloperidol (-5.82 & -8.87); the difference between treatments after 4 weeks of treatment approached statistical significance (-3.24, p=0.061). Statistically significantly more patients responded to treatment (defined a priori as ≥ 20% reduction in PANSS total score) in the quetiapine than the haloperidol group (52.2 vs 38.0%, p=0.043). All other secondary efficacy end points showed greater improvements with quetiapine than haloperidol (not statistically significant). Quetiapine was significantly better tolerated than haloperidol: fewer quetiapine patients required anticholinergics (44.3 vs 59.6%, p=0.011), had an increase in Simpson Scale score (23.9 vs 39.1%, p=0.005), experienced EPS-related adverse events (13.6 vs 30.5%, p<0.001). Fluphenazine elevated plasma prolactin, this was significantly reduced in the quetiapine compared with the haloperidol group (-601.39 vs -20.54 mU/ml, p≤ 0.001). Quetiapine would appear to be more effective, and better tolerated, than haloperidol in patients classed as partial responders.

Supported by a grant from Zeneca Pharmaceuticals

Poster No. 161

Strategies for Switching from Conventional Antipsychotic Drugs or Risperidone to Olanzapine

Bruce Kinon, M.D., Bruce Basson, M.S., Sandra Malcolm,B.S., and Alan Breier, M.D

Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana, 46285

Objective: Olanzapine, a novel antipsychotic drug (APD), offers an alternative treatment for out-patient schizophrenia patients who have received partial remission during conventional APD or risperidone treatment. This study was designed to facilitate the routine utilization of olanzapine by comparing the efficacy and safety of strategies relevant for switching patients from conventional APDs or risperidone to olanzapine.

Method: In this multi-site study, 209 outpatients with a diagnosis of schizophrenia or schizoaffective disorder and with documented clinical stability while treated with a conventional APD (n=139) or with risperidone (n=70) were openly randomized to either abrupt discontinuation or graduated withdrawal of their prior APD. Patients were further randomized in a double-blind fashion to receive either: a) olanzapine 10 mg QD for 3 weeks; or b) a sequence of one week each on placebo, olanzapine 5 mg QD, and olanzapine 10 mg QD. The efficacy of these 4 medication switching paradigms was assessed using the Clinical Global Impressions scale, Patients Global Impressions scale, and Positive and Negative Syndrome Scale. Safety assessments included ratings for extrapyramidal side effects, and treatment emergent adverse events.

Results and Conclusions: The strategy of gradual APD discontinuation combined with an initial full dose of olanzapine 10 mg showed the greatest efficacy and tolerability evident as early as week 1. None of the 4 switching paradigms was associated with overall clinical worsening. These data suggest that stable outpatients can be switched to olanzapine treatment, if indicated, without experiencing an increased vulnerability to relapse or to occurrence of clinically burdensome APD withdrawal symptoms.

This study was funded by Eli Lilly and Company.

Poster No. 162

Switching from Conventional Antipsychotics to Ziprasidone: An Interim Analysis of a 6-week Study

Peter Weiden, M.D.,[1] George Simpson, M.D.,[2] Thomas Kramer, M.D.,[3] Philip Harvey, Ph.D.,[4] Peter Powchik, M.D.,[5] and the Switch Study Group

[1] St Luke's/Roosevelt Hospital, Columbia University College of Physicians & Surgeons, 411 West 114th Street, Suite 3C, New York, NY 10025, USA
[2] LAC+USC Medical Center, Los Angeles, California, USA
[3] Little Rock, Arizona, USA
[4] Mt. Sinai School of Medicine, New York, USA
[5] Pfizer Pharmaceuticals Group, New York, USA

The aim of this study was to investigate the course of switching outpatients with schizophrenia who have efficacy problems or unacceptable side effects from their conventional antipsychotics to ziprasidone.

This was an interim analysis of a 6-week, randomized, blinded-rater study in which stable outpatients (n=68) were switched from their maintenance conventional antipsychotic medication to ziprasidone 40–160 mg/day.

At week 6, 65% of patients were rated as improved on the CGI-I. Mean PANSS total, positive, negative, and cognitive subscales and CGI-severity scores decreased significantly (P <0.05) from baseline. There were reductions in mean EPS movement disorder scores and a substantial decrease in the percentage of patients requiring anticholinergic medication. Significant improvements in cognitive function tests related to motor skill, planning, and to verbal learning and recall were also observed. The most frequent adverse events with ziprasidone included nausea, headache, somnolence and insomnia. Baseline prolactin levels decreased and body weight change was negligible.

The significant improvements in psychopathology and reductions in EPS without any additional weight gain were observed after 6 weeks of ziprasidone therapy. This study suggest that ziprasidone will be helpful for many "stable" outpatients who have persistent symptoms or EPS side effects on their current conventional antipsychotic.

Poster No. 163

Anticholinergic Differences Among Patients Receiving Standard Clinical Doses of Olanzapine or Clozapine

K. N. Roy Chengappa, M.D.[1, 2, 3], Bruce Pollock, M.D., Ph.D[1,3], Haranath Parepally, M.D.,[1,2], Joesph Levine, M.D., M.A.Sc.[1,3], Margaret Kirshner, B.A[1], Jaspreet Brar, M.D., M.P.H.[1], Rebecca Zoretich, M.Ed.[1,2]

1. Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, Pittsburgh, PA.
2. Special Studies Center at Mayview State Hospital, Bridgeville, PA.
3. Stanley Center for The Innovative Treatment of Bipolar Disorder, Pittsburgh, PA.

Presenting Author:
K. N. Roy Chengappa, M.D., F.R.C.P.C.
Associate Professor of Psychiatry
Western Psychiatric Institute & Clinic
Special Studies Center @ Mayview State Hospital
Stanley Center for the Innovative Treatment of Bipolar Disorder
3811 O'Hara Street
Pittsburgh, PA 15213-2593

Objective: The authors' goal was to evaluate anticholinergicity among patients with schizophrenia, schizoaffective or bipolar I disorder who were receiving either olanzapine (n = 12) or clozapine (n = 12) at standard clinical doses.

Method: Serum anticholinergic levels were determined in adult men and women subjects using a radioreceptor binding assay. The UKU scale (Udvalg for kliniske undersogelser) was used to evaluate anticholinergic side effects clinically, and the Mini-mental state examination (MMSE) provided a global cognitive measure. Patients had achieved target doses that were stable at the time of the blood draw, and no other concomitant medicine with known anticholinergic potential was allowed. ***Results:*** Patients receiving olanzapine (average dose - 15 mg/

day) had serum anticholinergic levels of 0.96 (± 0.55) picomols/mL atropine equivalents as compared to 5.47 (± 3.33) picomols/mL for those receiving clozapine (average dose - 444 mg/day), $p < 0.001$. Increased and decreased salivation were significantly more common among the clozapine and olanzapine treated patients respectively, whereas constipation, urinary disturbances, and tachycardia/palpitations were significantly more common among clozapine treated subjects. Neither group showed any global cognitive deficits. ***Conclusions:*** Olanzapine treated patients had less than one-fifth the anticholinergic levels in serum as compared to clozapine treated patients. These *in vivo* results are in contrast to those reported previously using an *in vitro* assay. Furthermore, clinical evaluations confirmed that clozapine treated subjects

experienced more frequent and severe anticholinergic side effects (except dry mouth). However, none of the patients in either group expressed any desire to quit these medicines due to anticholinergic side effects.

Acknowledgments: Partial support of the study by a grant from Lilly Research Labs, The Stanley Center for the Innovative Treatment of Bipolar Disorder @ the University of Pittsburgh, and NIMH grants MH 55106, MH 01509 and MH 52247.

Poster No. 164

Iron and Neuroleptic-Induced Parkinsonism in Schizophrenic Patients

Ileana Berman1,2, David Klegon1, Roger Bayog1, Catherine Chmiel2, Alan I. Green1,

Donald Goff1, Miklos F. Losonczy3

1)Consolidated Department of Psychiatry, Harvard Medical School; 2)Taunton State Hospital, 60 Hodges Ave, Taunton MA 02780; 3) Mount Sinai School of Medicine, N.Y.

Introduction: Iron has long been implicated in the etiology of central nervous system diseases and more recently has been shown to play a role in some neuroleptic-induced movement disorders. There are reports, for example, suggesting an association between iron and neuroleptic-induced akathisia, acute dystonic reactions, and neuroleptic malignant syndrome. However, the possible relationship between serum iron levels and neuroleptic-induced parkinsonism is yet unknown. This study, for the first time, examines the relationship between neuroleptic-induced parkinsonism and serum iron in a group of chronic schizophrenic patients treated with stable doses of antipsychotics. As a secondary aim, we examined the relationship between iron and tardive dyskinesia (TD).

Method: A total of 41 male patients participated in this study. All subjects met criteria for chronic schizophrenia according to DSM III-R and had been treated with the same dose neuroleptics for at least two weeks prior to assessments which included the Simpson Angus scale, the Abnormal Involuntary Movement Scale (AIMS), and the Barnes Akathisia Scale, and blood assays for serum iron, total iron binding capacity (TIBC), transferrine, and ferritin. Those with anemia, medical illnesses known to interfere with iron metabolism, or akathisia (on examination) were excluded.

Results: Compared to the non-parkinsonism group, the parkinsonism group had significantly lower levels of both serum iron ($t=-2.4$, $p<0.04$, $df=35$) and TIBC ($t=2.17$, $p=0.02$, $df=32$). In addition, ferritin levels were higher in the parkinsonism group at a trend level of significance ($t=-1.9$, $p=0.06$, $df=23$). Since age differed between the two groups and since the degree of parkinsonism can be affected by the neuroleptic dose, we performed an analysis of variance in which age and chlorpromazine (CPZ) equivalent dose were used as covariates. The parkinsonism group continued to show significantly lower levels of TIBC ($F=4.6$, $p=0.04$) and a trend toward lower iron levels ($F=3.1$, $p=0.08$). The severity of parkinsonism correlated inversely with serum iron concentrations ($r=-0.42$, $p=0.009$, $df=35$) and TIBC ($r=-0.37$, $p=0.04$, $df=30$). We found no significant correlations between parkinsonism scores and ferritin levels ($r=0.09$, $p=0.64$, $df=25$). We performed a multiple regression analysis in which we first entered age and the CPZ equivalent dose followed by serum iron concentrations, TIBC, ferritin, and transferrine. Parkinsonism scores continued to show an association with the plasma iron ($F=4.2$, $p=0.01$) and a trend towards an inverse correlation with TIBC levels. We found no association between serum iron and TD scores.

Conclusions: These results support previous findings suggesting that iron plays a significant role in the etiology of neuroleptic-induced movement disorders. However, it is unclear whether the alterations in the iron metabolism are predisposing factors to the development of parkinsonism or rather associative manifestations of neuroleptic-induced parkinsonism. Interestingly, these iron alterations resemble those seen in chronic disorders, such as inflammatory diseases, infectious disorders and cancer.

Poster No. 165

Neuroleptic Dose Requirements and Treatment Response in Schizophrenic Patients Comorbid for Substance Abuse

Nehal Vadhan, MA[1], Jamie Elliot,[2] Caroline Lerner,[2]
Nadine Chang,[2] Danielle Richarme,[1]
James C. -Y Chou, MD[2] & Mark Serper, Ph.D.[1,2]

[1]Department of Psychology, Hofstra University, Hempstead, NY 11549-1270
[2]NYU School of Medicine, New York, NY

Introduction: The effects recent substance abuse has on schizophrenic patients' clinical course remains unsettled because past reports have yielded conflicting findings. Some investigators, for example, find schizophrenic patients with comorbid substance abuse have an exacerbated course of illness and require higher doses of neuroleptic medication. Others, in contrast, report substance abuse has little to mild effects on schizophrenic patients' treatment response and outcome. Possible reasons for past inconsistent findings include retrospective study designs and a lack of specification of class of abused drug.

Method: The present study avoids some past methodological concerns by prospectively examining medication dose requirements and treatment response in a group of schizophrenic patients comorbid for cocaine abuse (SZ+COC; n = 46) and a group of non-substance abusing schizophrenic patients (SZ; n = 64). All patients were administered the BPRS within 48 hours of arrival to the Bellevue Hospital Psychiatric Emergency Service (T1) and again at Week 4 of inpatient treatment (T2). Medication dose was studied naturalistically on inpatient units at both assessment time points and treatment response was defined by a 20% improvement in overall BPRS scores from T1 to T2 assessments.

Results: SZ+COC patients showed increased global BPRS psychopathology at T2 compared to SZ patients ($p < .05$). No group differences, however were detected in the rate of neuroleptic treatment improvement from T1 to T2 ($p > .05$). Results also indicated that SZ+COC patients were administered significantly more neuroleptic medication by T2 compared to SZ patients ($p < .01$).

Conclusions: These results are discussed in terms of the neurobiological impact of acute cocaine cessation on schizophrenic symptoms and neuroleptic treatment response.

Supported by a NARSAD Young Investigator Award.

Poster No. 166

Algorithms for Treating Anxiety in Patients with Chemical Abuse and Dependence

David Osser, M.D.[1] and Rogelio Bayog, M.D.[2]

[1]Department of Psychiatry, Harvard Medical School at the Brockton VA Medical Center, 940 Belmont Street, Brockton, MA 02401 [2]Harvard Medical School, Taunton State Hospital, MA

The use of pharmacotherapy in these patients presents some special problems that have not been addressed systematically in previously published algorithms for the treatment of anxiety disorders. The authors surveyed the literature and expert opinion, giving priority to first-quality research studies. The initial algorithm drafts (flowcharts and texts) were reviewed by a panel of four local experts and presented at several public meetings for additional suggestions.

To be eligible for entry into the algorithm, patients must have completed withdrawal from their drug(s) of dependence and any pharmacotherapy this might require and be abstinent for at least one additional week. General medical screening occurs. If the patient was alcohol dependent, and the patient's anxiety may be due to preoccupation with or craving for alcohol, consideration of a trial of naltrexone is recommended. If not, or if anxiety symptoms persist following this, algorithm pathways are available for each major DSM-IV anxiety disorder.

For Panic Disorder, the first-line recommendation is for an SSRI or nefazodone plus appropriate psychotherapy. Benzodiazepines are generally not recommended, either as monotherapy or adjunctively, but a list of exceptions is proposed. The second-line suggestion is a second SSRI but consider venlafaxine, mirtazapine, or a tricyclic (if not high suicide or seizure risk). The third-line emphasizes the last three options. Fourth-line would be valproate if persistent liver disease is not a problem, or various combination treatments.

Social Phobia, Generalized type: If there is comorbid depression, SSRIs or possibly nefazodone are first-line. If not, cognitive behavioral therapy or SSRIs are suggested. Benzodiazepines are usually not recommended. Second-line would be another SSRI/nefazodone. Third-line would be augmentation with buspirone or a third SSRI/nefazodone, but consider clonazepam, gabapentin, venlafaxine, and certain others.

PTSD: This complex algorithm first requires appropriate psychotherapy to be available. Then those with comorbid depression are offered SSRIs or nefazodone first-line. Those without depression but with insomnia may receive a trial of a hypnotic (e.g. - trazodone). After that, an antidepressant is proposed. If PTSD-related psychosis is present, an antipsychotic might be tried next, or then another antidepressant trial. Those still symptomatic with hyperarousal symptoms may be given clonidine, and those with impulsivity and aggression may receive mood stabilizers.

OCD: Two or three monotherapy trials with SSRIs, at higher doses if necessary, are proposed. Clomipramine may be less safe in this population. Among the augmentations, buspirone and antipsychotics may have slight priority in this population.

GAD: Generally the comorbid problems receive treatment priority. The first-line pharmacotherapy is buspirone, followed by antidepressants. Venlafaxine has particular support.

Poster No. 167

Utility and Medication Interaction of Combined Naltrexone Fluoxetine Treatment in Depressed Alcoholics: A Pilot Study

Ihsan M. Salloum; Jack R. Cornelius; Dennis C. Daley; Levent Kirisci; Crystal R. Spotts.
University of Pittsburgh School of Medicine, Department of Psychiatry, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213.

Background: The aim of this study is examine the utility of naltrexone, fluoxetine in decreasing alcohol use in patients with comorbid alcohol dependence and major depressive disorders and to examine medication interaction between naltrexone and fluoxetine. Specifically, we examined whether there is a clinically significant change, defined as a 20% to 40% increase, in fluoxetine/norfluoxetine serum concentration when naltrexone is added on to fluoxetine after the latter medication and its metabolite, norfluoxetine, have reached a steady states of serum concentration.

Methods: Subjects with DSM-IV/SCID diagnoses of comorbid alcohol dependence and major depressive disorder, who were free from any other medical, psychiatric, or other substance use disorders, and who were not taking any other medication or over the counter drugs, were enrolled in the study. Subsequent to comprehensive evaluation, alcohol detoxification and assessments, subjects were started on fluoxetine (20 mg/day). Naltrexone 50mg/day dose was added only after subjects have been on stable fluoxetine dose for 6 weeks. Fluoxetine/norfluoxetine serum concentration measurement were determined at week 6 and at week 7 (to document the steady state status of the serum concentration) and were repeated at week 10 and at week 11.

Results & Significance: Drinking outcome for 9 subjects, as measured by the Timeline Method, decreased from an average of 59.56 (sd=34) drinks per week at baseline to 11 (sd=15) drinks per week at the end of the study ($t=3.426$, $df=8$, $p=0.009$). Depressive symptoms, as measured on the Hamilton Rating Scale for Depression decreased from an average of 20.44 (sd=8.53) to 10 (sd=7.97) at the end of the study ($t=2.860$, $df=8$, $p=0.021$).

Six subjects have completed the medication interaction studies to date. There were no changes in the fluoxetine/norfluoxetine serum levels in four subjects. Only one subject had an increase of 20% or more of both fluoxetine and norfluoxetine blood levels and one subject had an increase of norfluoxetine, but not fluoxetine blood levels above 20% after adding naltrexone. There were no clinically significant side effects reported by these two subjects after starting naltrexone. Combination medications were well tolerated by all subjects, and no adverse reactions were reported for any subject on combination medication. The results of this pilot study suggest that combined fluoxetine and naltrexone may be useful in decreasing both the depressive symptoms and alcohol use among depressed alcoholics. The results also suggest that naltrexone may not increase fluoxetine or norfluoxtine blood levels in most patients.

Poster No. 168

Effect of Buprenorphine on CYP3A Activity in Rat Liver Microsomes

Rami B. Ibrahim, R.Ph. [1], Jacquelyn G. Wilson Pharm.D.[1,2], David J. Edwards, Pharm.D. [1]

[1]Wayne State University, College of Pharmacy & Allied Health Professions, Department of Pharmacy Practice, 328 Shapero Hall Room 328, Detroit, MI 48202.
[2]Wayne State University School of Medicine, Department of Psychiatry, Detroit, MI 48202

Buprenorphine is a partial opioid agonist available in France as an alternative to methadone in the treatment of opiate-dependent individuals. Twenty deaths have been reported in patients taking buprenorphine in combination with benzodiazepines. Since buprenorphine and many benzodiazepines are CYP3A substrates, the effect of buprenorphine on CYP3A activity was examined in order to assess the likelihood of a pharmacokinetic interaction. The formation of 6β-hydroxytestosterone was measured in dexamethasone-induced rat liver microsomes under control conditions and in the presence of buprenorphine. Buprenorphine was found to be a weak inhibitor of CYP3A with a concentration of 150 μM required for a 50% decrease in enzyme activity. Since this is more than 2000 times higher than typical plasma concentrations in humans, buprenorphine is unlikely to cause clinically significant inhibition of CYP3A in patients. Excessive CNS depression due to the combination of buprenorphine and benzodiazepines is most likely due to additive or synergistic pharmacologic effect.

Poster No. 169

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Poster No. 170

Valproate Treatment of Bipolar Depression

Frederick Petty, Ph.D., M.D., Martin Kram, M.D., Lori L. Davis, M.D., Alexandria Nugent, M.eD., Michele Bollig. R.N., Virginia Gajewski, R.N., Gerald L. Kramer, B.A.

Veterans Affairs Medical Center, University of Texas Southwestern Medical Center, Dallas, Texas

Although valproate is widely used for the treatment of mania, it had not been systematically investigated in the depressed phase of bipolar disorder. We tested the clinical efficacy of valproate (divalproex, Depakote®) for bipolar depression in an eight week, double blind, placebo controlled randomized clinical trial in 27 outpatients with bipolar depression. Valproate was more effective than placebo in improving symptoms of depression in this sample ($p = 0.02$), and valproate also resulted in significantly greater improvement in symptoms of anxiety than placebo ($p = 0.009$). Valproate was generally well tolerated. Since valproate is a GABA agonist, finding clinical efficacy for valproate in both the manic and depressed phases of bipolar disorder supports the GABA dysequilibrium theory of mood disorders.

Poster No. 171

Is Methylphenidate Like Cocaine? Subjective Effects in Cocaine Dependent Volunteers

Robert Baker, M.D.[1], Craig Rush, Ph.D.[1], and Eric Warren, M.D.[1]

[1]University of Mississippi Medical Center, Department of Psychiatry and Human Behavior, 2500 North State Street, Jackson, MS 39216

Background: Methylphenidate and cocaine have similar pharmacologic actions, including comparable affinity for the dopamine transporter. Animal studies suggest reinforcing effects for methylphenidate as well as cocaine; for example, in one self-administration choice study, rhesus monkeys equally preferred equal doses of methylphenidate and cocaine. Human laboratory subjective-effects studies have yielded mixed predictions of methylphenidate's abuse potential, with some authors concluding that methylphenidate's relatively slow uptake and clearance limit its abuse potential.

Methods: We measured relative subject-rated effects of a range of doses of oral cocaine HCl (50, 100, 200, and 300 mg) and methylphenidate (15, 30, 60, and 90 mg), using both a placebo control and an active control (triazolam 0.125, 0.25, 0.5, and 0.75 mg). Subjects were six hospitalized volunteers, healthy except documented recent use of crack cocaine. Subjects participated in one experimental session daily during which they received one dose of study medicine. Before the dose and at repeated intervals post-dosing, subjects completed a battery of subjective and objective measures of drug effects.

Results: The tested drugs were well-tolerated. Cocaine and methylphenidate produced comparable dose-related effects in a series of subjective measures such as "drug liking", "good effects", "willing to take again", and "willing to pay for". Placebo and triazolam produced distinctly different subjective effects than cocaine or methylphenidate.

Significance: Stimulant drugs may show more laboratory evidence of abuse liability in cocaine-abusing volunteers than in non-abusing subjects. Our laboratory has demonstrated the discriminative and reinforcing effects of oral cocaine as studied in crack cocaine smokers. The present experiment did not directly assess reinforcing effects of methylphenidate, but the subjective-effects results are quite similar to oral cocaine. This suggests that in this population, methylphenidate has significant abuse potential. This warrants caution and further study regarding methylphenidate prescription to patients with history of cocaine abuse.

Funded by NIH/NIDA R01 DA 10325 (Rush)

Poster No. 172

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Poster No. 173

Abstract Title: ADHD, Stimulant Medications, and Parents Perception of Sleep Difficulty: Is there a relationship?

Lisa Efron, Ph.D. [1], Marina Broitman, M.Phil. [1], Phillip Pearl, M.D. [2], Ellen Hamburger, M.D.,[3] & Mark Stein, Ph.D.[1]

[1] Department of Psychiatry and Behavioral Sciences; Children's National Medical Center and The George Washington University Medical School; 111 Michigan Avenue, NW; Washington, DC 20010
[2] Department of Neurology; Children's National Medical Center and The George Washington University Medical School; Washington, DC
[3] Department of Pediatrics, George Washington University Medical School; Washington, DC

BACKGROUND: There are strong associations between sleep problems and psychopathology in adults, and anecdotal reports indicate that sleep problems are frequently associated with ADHD. Insomnia and other sleep problems are commonly reported as side effects of stimulant medications, frequently used to treat ADHD. The purpose of the present study is to compare the prevalence of sleep problems in children with ADHD with normal controls, and examine if stimulant medications are associated with parent perceptions of children's sleep difficulties.

METHODS: We investigated parental perceptions of sleep problems in 111 4-18 year old children (M=9.2, SD=3.7) referred to an ADHD clinic and 90 pediatric outpatients. Parents of children in both groups were administered a sleep questionnaire developed by the investigators, the Achenbach Child Behavior Checklist (CBCL), and a medical history questionnaire. The 28-item-sleep questionnaire assessed the presence and severity of a variety of sleep problems, practices, and interventions.

RESULTS: In the ADHD group, 48% of parents (n=62) reported that their children took more than 30 minutes to fall asleep at least one night a week, compared to 21% of parents of children from the pediatric control group (n=84; X^2=17.05; p=.002). Of the ADHD group, 26% of children who were taking stimulant medications took more than thirty minutes to fall asleep at least once a week, compared to 19% of children not taking stimulants (X^2=11.37, ns). Moreover, 40% of the ADHD sample (n=65), were described as "tired during the day" at least once a week, compared to 27% (n=85) of the pediatric outpatients (X^2=4.25, ns). Children referred to the ADHD clinic (n=89) experienced more severe sleep problems overall per parent report, than did children attending appointments at the general pediatric clinic (n=88; t=2.23, p<.05). Within the ADHD clinic sample, children diagnosed with ADHD Combined subtype (n=24) experienced more severe sleep problems overall than did children diagnosed with ADHD Inattentive subtype (n=8; t=2.54, p<.05).

SIGNIFICANCE: These results highlight the importance of assessing sleep problems prior to initiating a medication trial in children with ADHD. Children with ADHD were almost twice as likely to display insomnia relative to controls, according to their parents. Future research attention should be directed towards validating parental perceptions of their children's sleep disturbances and the effects of different stimulant and dose response relationships.

Poster No. 174

CLINICIAN, PARENT, AND CHILD PREDICTION OF MEDICATION OR PLACEBO IN DOUBLE-BLIND DEPRESSION STUDY

Carroll W. Hughes, Ph.D.[1,2], Jeanne Rintelmann, B.A.[1], Graham Emslie, M.D.[1], Robert Kowatch, M.D.[1], Warren Weinberg, M.D.[1], A. John Rush, M.D.[1]
[1]University of Texas Southwestern Medical Center - Dallas
[1,2] Terrell State Hospital, P.O. Box 70, Terrell, TX 75160

In a randomized, double blind study of 96 patients, fluoxetine was found to be superior to placebo in the acute phase treatment of major depressive disorder in child and adolescent outpatients (Emslie et al, *Arch Gen Psychiatry*, 1997; 54:1031-1037). One issue of concern to double blind studies is how well the blind is maintained over the course of the study as the investigators become more familiar with the treatment outcomes. Can clinicians accurately predict drug versus placebo response? A secondary question of interest is how well the subjects or their parents could predict which treatment they had received following 8 weeks of treatment. Was there a relationship between what they had received and their perception of clinical response? We report here the findings of these predictions.

Method: Ninety-six child and adolescent outpatients (aged 7-17) with nonpsychotic major depressive disorder were randomized to 20 mg of fluoxetine or placebo. They were seen weekly for 8 consecutive weeks preceded by 3 evaluation visits that included structured diagnostic interviews and a 1-week, single-blind placebo run-in. Primary outcome measurements were the CGI and the CDRS–R. At the end of 8 weeks a clinician (and in some cases an additional blind rater), the parent(s), and the child were asked to indicate whether they thought the child had been on placebo or active medication using a random subsample of this original population distributed over the 4 year course of the study. If patients were determined to be responders they were encouraged to remain blind and on whatever treatment that they had been receiving. In no case was blind broken for treating/rating clinicians (Emslie et al, *J Amer Acad Child Adolesc Psychiatry*, 1997, 36(6): 785-792). Non-responders were treated open label for an additional period or switched to an alternative medication.

Results: *Clinicians.* When subjects on both active treatment and placebo were combined, clinicians' prediction of on either active medication or placebo did not differ from chance ($C^2 = 0.01$, $p = .92$). When medication and placebo were tested separately, clinicians were able to accurately predict that responders had been on medication 79% of the time ($C^2 = 3.8$. $p = .05$), but not placebo. *Parents.* Unlike the clinicians, when subjects on both active treatment and placebo were combined, parents' predictions were significant ($C^2 = 16.0$, $p < .001$). When medication and placebo were tested separately, parents of responders were able to predict 82 % of the time that they had been on medication, ($C^2 = 4.6$, $p < .03$), and 89% for placebo ($C^2 = 11.5$, $p < .001$). *Child/Adolescent Subjects.* Similar to the parents, when subjects on both active treatment and placebo were combined, the subjects' predictions were significant ($C^2 = 16.7$, $p < .001$). When medication and placebo were tested separately, the responder subject was able to predict 81% of the time that they had been on medication ($C^2 = 3.6$, $p = .05$), and 90% for placebo ($C^2 = 14.9$, $p < .001$).

Conclusions: Both parents and child/adolescent subjects when they have responded positively to treatment, appear to predict better than clinicians whether they have been on active medication or placebo. However, important for design integrity is the finding that clinicians do accurately predict when somebody has been on medication with a positive response while prediction remains at a chance level for

non-response. The prediction of placebo or not for clinicians remains at chance level whether response or non-response.

This study was supported by grants MH-39188 (GJE) and MH-41115 (Dept of Psychiatry, UT Southwestern Medical Center at Dallas) from the NIMH.

Poster No. 175

WHO KNOWS BEST – MOTHERS OR OTHERS? COMPARING BIOLOGICAL MOTHERS VS. CHILD SELF REPORT TO OTHER PRIMARY CARETAKERS VS. CHILD SELF REPORT ON A NEW STRUCTURED DIAGNOSTIC INTERVIEW IN A MINORITY SAMPLE

Amy B. Rowan, M.D.[1,2]; LaTanya McLean, B.S.[1]; Michèle Muñoz-Miller, B.A. [1]; Jennifer Schecter, B.S. [1]; Charles Keller, B.A[1]; Ronald Weller, M.D.[2]; Elizabeth Weller, M.D.[1,2]

[1] The Children's Hospital of Philadelphia, 34th and Civic Center Blvd, Philadelphia, PA 19104

[2] The University of Pennsylvania, Philadelphia, PA

Background: Most structured interviews focus on the mother as primary reporter, and there is little information on the agreement between other guardians and children's reports. This study examines agreement between the Children's Interview for Psychiatric Syndromes (ChIPS) and its parent version (P-ChIPS) in a large, clinical, outpatient African-American sample. Specifically, the percent agreement between children (ChIPS) and their biological mothers (P-ChIPS) was compared to the percent agreement between children and other P-ChIPS informants (i.e., Father, Foster Mother, Grandparents, other relatives).

Method: Two trained interviewers administered ChIPS and P-ChIPS to children (ages 6-17) and guardians, respectively, alternating the order of ChIPS and P-ChIPS performed by each. Interviews deemed clinically invalid were eliminated. P-ChIPS/ChIPS pairs were separated for analysis based on who completed the P-ChIPS interviews: pairs in which biological mothers had completed the P-ChIPS interview were separated from and compared with a group consisting of all other P-ChIPS informants and their ChIPS pairs. Mother/Child pairs and Other/Child pairs were matched based on the children's ages and genders. The percent agreements for the 74 resultant pairs (37 Mother/Child pairs and 37 Other/Child pairs) were then calculated and compared.

Results: For both Mother/Child pairs and Other/Child pairs (of those that were matched by children's ages and genders), there was very good to excellent agreement (>70%) found for Attention Deficit Disorder (Inattentive Type), Attention Deficit/Hyperactivity Disorder (Hyperactive Type), Conduct Disorder (Moderate and Severe Types), Substance Abuse, Specific Phobia (All Types), Social Phobia, Generalized Anxiety Disorder, Obsessions, Compulsions, Obsessive-Compulsive Disorder (Combined Type), Post-Traumatic Stress Disorder, Acute Stress Disorder, Anorexia Nervosa, Bulimia Nervosa, Manic Episode, Hypomanic Episode, Enuresis, Encopresis and Schizophrenia. Agreement for all other diagnoses was as follows: Attention Deficit/Hyperactive Disorder – Combined Type (Mother/Child – 70%, Other/Child – 68%); Oppositional Defiant Disorder (Mother/Child – 57%, Other/Child – 73%); Mild Conduct Disorder (Mother/Child – 81%, Other/Child – 68%); Separation Anxiety (Mother/Child – 54%,

Other/Child – 49%); Major Depressive Disorder (Mother/Child – 70%, Other/Child – 59%); and Dysthymia (Mother/Child – 59%, Other/Child – 76%).

Conclusion: Overall, the results suggest that there are no notable differences in percent agreement as a function of P-ChIPS informant. This suggests that the P-ChIPS interview is equally as sensitive to biological mothers as to other primary caretakers or guardians. Although many children presenting to the clinic were from single parent homes, there were a large number of children whose extended families were very involved. The flexibility of the P-ChIPS interview, by supporting its use with the child's primary caregiver, makes it a useful tool in assessing psychopathology in children from various living situations.

Poster No. 176

Psychiatric Illness in Mothers who Bring Children for Mental Health Care

M. Katherine Shear M.D.[1], Catherine Greeno Ph.D.[1] and Carol Anderson Ph.D.[1]

[1] University of Pittsburgh SOM, 3811 O'Hara Street, Pittsburgh, PA 15213

Aims: To study diagnosis and treatment seeking among mothers who bring children for mental health care.
Significance: There are reasons to expect that untreated psychiatric disorders are prevalent in mothers of ill children. Genetic factors are well
documented in anxiety and depressive disorders. Common environmental factors may also comprise risk factors. Research findings suggest psychopathology in mothers is associated with maladjustment and illness in children, yet ill mothers are likely to put the needs of the children before their own.
Procedures: We are conducting a study in a rural community mental health child treatment center. We report here interim results of 55 consecutive consenting biological or adoptive mothers and their children interviewed by trained raters using structured clinical interviews to establish maternal (SCID) and child (KSADS) DSM IV diagnoses. Mothers also completed questionnaires, assessing symptoms, functional impairment, social support, partner abuse, personality functioning, and burden of care.
Results: 73% (n=40) mothers met DSM criteria for current illness, as did 76% of children. Maternal diagnosis was present 7 of the 13 children without a diagnosis. Major depression (n=24) was the most common primary maternal diagnosis. Most diagnosed mothers (n=25) met criteria for 2 or more current diagnoses. The majority were not receiving any treatment. Mothers with diagnoses scored significantly higher on measures of symptoms and functional impairment, higher on caregiver burden and partner abuse and lower on social support. Unlike prior studies, diagnosed mothers did not report more problems in children on the Child Behavior Check List. We conclude that women who bring their children for mental health treatment are a high risk, under-treated group.

This work was supported by MH-56848.

Poster No. 177

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Poster No. 178

Prescribing Pattern for Antidepressant Pharmacotherapy, Diagnosis of Depression, and Receipt of Psychotherapy Among Children and Adolescents: 1990-1995

David A. Sclar, B.Pharm., Ph.D.,[1,2] Linda M. Robison, M.S.P.H.,[1] Tracy L. Skaer, B.Pharm., Pharm.D.,[1] Richard S. Galin, M.D.[3]

[1]Pharmacoeconomics and Pharmacoepidemiology Research Unit, College of Pharmacy, Washington State University, P.O. Box 646510, Pullman, WA 99164-6510

[2]Washington Institute for Mental Illness Research & Training, Eastern Branch, Spokane, WA

[3]Neuro-Psychiatric Institute, University of California at Los Angeles, Los Angeles, CA

Background and Objectives: To date, the FDA has not approved antidepressant pharmacotherapy for the treatment of depression in persons less than 18 years of age. Herein, we explore both antidepressant utilization and the prevalence and treatment of depression at the national level among children and adolescents age 5-18 years. Specifically, we discern: (*i*) the rate of physician-patient encounters (office-based visits) which document the use of antidepressant pharmacotherapy, and reason (ICD-9-CM code); (*ii*) the rate of office-based visits which document a diagnosis of depression, and the proportion of these patients with concomitant mental disorders; and (*iii*) the proportion of patients with a diagnosis of depression receiving psychotherapy, antidepressant pharmacotherapy, the combination, or no treatment.

Methods: Data from the National Ambulatory Medical Care Survey (NAMCS) for the time-frame 1990 through 1995, were used for this analysis.

Results: An estimated 4,638,608 office-based visits documented the prescribing of antidepressant pharmacotherapy for any reason among children and adolescents between 1990 and 1995; a rate of 9.0 per 1,000 office visits, and 15.2 visits per 1,000 U.S. population age 5-18 years. Depression was the most common diagnosis (42.8%) among patients prescribed an antidepressant, followed by attention-deficit hyperactivity disorder (18.5%), and neurotic disorders (7.4%).

A total of 4,115,104 office-based visits resulted in a diagnosis of depression over the time-frame. Among these depressed patients, 36.2% had a concomitant mental disorder. Nearly half (48.2%) were prescribed an antidepressant. The rate of a diagnosis of depression was 8.0 per 1,000 office visits, and 13.6 per 1,000 U.S. population; a diagnosis of depression in concert with the prescribing of antidepressant pharmacotherapy was 3.9 per 1,000 office visits, and 6.6 per 1,000 U.S. population.

Among patients with a diagnosis of depression 19.4% received neither psychotherapy nor an antidepressant regimen; 11.0% were prescribed antidepressant pharmacotherapy alone; 34.8%

received psychotherapy alone; and 34.8% received both psychotherapy and antidepressant pharmacotherapy (psychotherapy data available for 1990-92, 1995 only).

Conclusions: The prevalence rates as documented in this study indicate that further research is essential to assess the safety and efficacy of antidepressant use among children and adolescents. Additionally, research on the combined efficacy of antidepressants and psychotherapy for depression is urgently needed.

This study was supported by the Pharmacoeconomics and Pharmacoepidemiology Research Unit.[1]

Poster No. 179

Significance of Expressed Emotion in Drug Trial of Adolescent Depression

Philippe Weintraub, M.D.[1] and Donald Rojas, Ph.D[1]

[1]UCHSC; Box C259-34; 4200 E. 9th Ave; Denver, CO 80262

Background: Most controlled studies have failed to show efficacy of medication in depressed adolescents. One possible explanation for these findings is the adverse effect of family stressors on drug response. This issue is being examined in an open label study of fluvoxamine in adolescent depression using parental expressed emotion (EE) as a measure of family dysfunction. Defined as excessive criticism or emotional overinvolvement directed towards a mentally ill relative, high EE has been associated with relapse in both adult and pediatric psychiatric disorders. It is hypothesized that depressed youth from high EE families will show a significantly worse response to fluvoxamine than those from low EE families.

Methods: Pilot data on the initial seven subjects beginning the assessment were analyzed. Subjects ranged in age from 12-17 years old. They all met criteria for major depression on the Child and Adolescent Psychiatric Assessment (CAPA). Functioning was assessed using the Child Global Assessment Scale (CGAS). Parental EE was assessed at the first visit with the Five Minute Speech Sample (FMSS), which was scored by raters blind to subjects' clinical status. The Family History Research Diagnostic Criteria (FH-RDC) was administered to exclude subjects with bipolar first degree relatives. Entry into the drug trial required scores of ≥ 12 on the Hamilton Depression Rating Scale (HAM-D) and ≥ 40 on the Child Depression Rating Scale-Revised (CDRS-R).

Results: There were 2 high EE and 5 low EE families. At baseline, subjects from high EE families had significantly higher rates of comorbid disruptive behavior disorders, school nonattendance, and parental depression. There was also a strong trend for high EE subjects to have severe functional impairment.

Both high EE subjects had poor clinical outcomes. One refused to complete the assessment. The other improved sufficiently to no longer be eligible for the drug trial, but his family refused outpatient follow-up. Within two months, he was hospitalized with a recurrence of his symptoms.

Four of the five low EE families successfully completed the assessment and sought out treatment recommendations at its conclusion. Of the four subjects who completed the assessment, two were excluded from the drug trial because of symptom improvement. The other two low EE subjects entered the drug trial of fluvoxamine (Luvox) and fully complied with the protocol; both of them have remained in treatment with resolution of symptoms in the year after the ending of their participation in the drug trial.

Possible Significance: These preliminary findings are consistent with the study hypothesis that high parental EE is associated with decreased drug efficacy in adolescent depression. They suggest that future drug trials should examine the impact of family stressors on drug response and compliance. It also appears that depressed youth with family problems may be a more severely ill subgroup in need of both drug and psychosocial treatments.

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Poster No. 182

Development of the Tourette Disorder Scale (TODS)

David Sheehan, M.D., M.B.A.[1], Doug Shytle, Ph.D.[1], Mary Newman, B.A.[3],
Paul Sanberg, Ph.D., D.Sc.[2], Archie Silver, M.D.[1]

[1]Child Psychiatry Research Center, Department of Psychiatry and Behavioral Medicine, MDC-14, University of South Florida College of Medicine, 3515 East Fletcher Ave., Tampa, FL 33613

[2]Department of Neurosurgery and Neuroscience Program, University of South Florida, Tampa, FL
[3]Department of Psychology, University of South Florida, Tampa, FL

For many children and adolescents with Tourette Disorder (TD), the behavioral and emotional symptoms (BESs) can be more clinically troublesome than their tics. However, because tics comprise an important dimension of this neuropsychiatric disorder, most traditional treatment outcome studies have focused primarily on treating the tics. We believe this approach is problematic for at least two reasons. First, measures of tic frequency or those that are driven by tic frequency have a skewed distribution in nature, reflecting the waxing and waning of tic symptoms over time and the marked individual differences between patients. This limitation along with unclear diagnostic boundaries may help to explain why only two medications have ever been approved by the FDA for TD. Secondly, improvement of the tics is not always accompanied by parallel improvement in the BESs. This is particularly unfortunate in those children and adolescents whose BESs cause the greatest impairment. For these reasons, we decided to develop a scale based on symptom information received from parents of TD children as well as on scale properties that have been very sensitive in discriminating drug from placebo in adult psychopharmacology studies.

As part of an internet survey, we asked parents of TD children and adolescents about the occurrence and relative impairment (over tics) of thirty-two BESs. Eighty percent of parents surveyed stated that the BESs had caused more problems in their child's daily life over the past month than the tics alone. We then identified those BESs which met the following "key symptoms" criteria: 1) on average caused significant problems more than "Sometimes" and 2) were rated as a "top 10" problem by _ 25% of the group.

The Tourette Disorder Scale (TODS) is a 15-item scale comprising motor and vocal tics, obsessive compulsive symptoms and key BESs identified from our survey findings. While this scale has not yet been validated, a clinical study is currently underway in order to validate the scale within a multi-center double-blind placebo-controlled medication trial. Preliminary results regarding the psychometric properties of the scale (i.e. reliability and validity) will be presented at the meeting.

If the TODS proves to be a valid and sensitive measure of treatment effects in TD, it may open the door to identifying novel medications which are effective for more than one dimension of this neuropsychiatric disorder. Acknowledgment: This research was funded in part by NINDS (NS32067), Tourette Syndrome Association, Inc. and Layton BioScience, Inc.

Poster No. 183

SPECTROSCOPIC IMAGING IN PEDIATRIC OBSESSIVE COMPULSIVE DISORDER

Kate D Fitzgerald, B.A., Gregory J Moore, Ph.D., Frank P MacMaster, B.A., Ian B Wilds, B.A., Navid Seraji-Bozorgzad, B.A, David R Rosenberg, M.D.

Wayne State University School of Medicine, Department of Psychiatry and Behavioral Neurosciences, University Health Center 9B, 4201 St. Antoine, Detroit, MI 48201

Background: Neurobiologic abnormalities in the striatum are believed to be involved in the pathophysiology of obsessive compulsive disorder (OCD). Previous volumetric magnetic resonance imaging studies have identified decreased striatal volume in pediatric OCD patients, particularly in the putamen. Although OCD commonly arises in childhood and adolescence, few studies have examined striatal biochemistry in non-depressed, psychotropic-naive OCD patients near illness onset. **Methods**: In this study, N-acetyl-aspartate (NA), a putative marker of neuronal viability, creatine (Cr) and choline (Cho) levels were measured in left and right caudate and putamina using a multislice ^{1}H magnetic resonance spectroscopic imaging sequence with nominal resolution of 0.8 cc in 13 treatment-naive, nondepressed OCD outpatients (8-17 years) and 13 case-matched controls. **Results**: A significant reduction in NA/Cr + Cho was observed in the left putamen in OCD patients vs. controls. NA/Cr + Cho levels did not differ significantly between case-control pairs in the right putamen or the right and left caudate nuclei. **Conclusions**: These findings provide new evidence of functional neurochemical marker abnormalities in the putamen in pediatric OCD. Our results must be considered preliminary, however, given the small sample size. We are also examining additional brain regions including medial and lateral thalamus, ventral and dorsal prefrontal cortices, amygdala and hippocampus as well as measuring NA levels before and after paroxetine treatment; results of these investigations will also be presented.

This work was supported in part by the Joe Young Sr. Foundation and by grants from the National Institute of Mental Health (MH 01372), Rockville, MD and the National Obsessive Compulsive Foundation (Milford, CT).

Poster No. 184

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Poster No. 185

Body Dysmorphic Disorder in Children and Adolescents: Clinical Features and Treatment Response

Ralph S. Albertini, M.D. and Katharine A. Phillips, M.D.

Butler Hospital/Brown University School of Medicine, 345 Blackstone Blvd., Providence, RI 02906

BACKGROUND: Body dysmorphic disorder (BDD), a preoccupation with a nonexistent or slight defect in appearance, usually begins during adolescence. Reported cases indicate that, as in adults, BDD in children and adolescents may lead to impaired functioning, psychiatric hospitalization, and suicide attempts. Several case reports suggest that SRIs may be effective in decreasing BDD symptoms and improving functioning in children and adolescents. Nearly all of the literature on BDD in children and adolescents, however, consists of case reports. In this study, we systematically assessed BDD's clinical features and treatment response in this age group in the largest series to date.

METHODS: 33 consecutive children and adolescents with DSM-IV BDD were assessed for demographic characteristics, phenomenology, associated psychopathology, and treatment history and response. Subjects ages 12-17 were assessed with the SCID-P; those ages 6-11 were assessed with the K-SADS-PL. Other scales used included the adolescent version of the Brown of Assessment Beliefs Scale and the BDD Data Form. Treatment response was assessed with the CGI.

RESULTS: Of the 33 children and adolescents, 3 were male and 30 were female. They had a mean age of 14.9 ± 2.2 years (range=6-17 years). The mean age of onset of BDD was 11.8 ± 2.6 years (range=5-17 years). Bodily preoccupation focused on a wide variety of body parts, most often the skin (61%) and hair (55%). 50% of the subjects had appearance-related beliefs that were delusional, and 79% had ideas or delusions of reference due to BDD. All subjects had associated compulsive behaviors, most often camouflaging (e.g., with clothing) in 94%, comparing with others (87%), and mirror checking (85%). 94% of subjects reported impairment in social functioning and 85% in academic functioning due to BDD, with 18% dropping out of school due to BDD symptoms. 39% had been psychiatrically hospitalized, 67% had experienced suicidal ideation, and 21% had made a suicide attempt. The most common comorbid lifetime diagnoses were major depression (73%), OCD (39%), and social phobia (30%).

Ten (53%) of 19 subjects treated with an SRI had much or very much improvement in BDD symptoms, and 10 (45%) of SRI trials led to much or very much improvement in BDD symptoms (7 of 12 fluoxetine trials, 1 of 4 paroxetine trials, 1 of 4 sertraline trials, 1 of 1 clomipramine trials, and 0 of 1 fluvoxamine trials). Six (43%) of 14 SRI trials in delusional patients led to much or very much improvement. Mean time to response was 8.0 ± 3.9 weeks (range = 4-16 weeks). In contrast, 0 of 8 trials with other psychotropic medications, 0 of 1 trials

of cognitive-behavioral therapy, 0 of 2 group therapies, and 1 of 20 psychotherapy treatments resulted in improvement. Twelve (36%) subjects received surgical, dermatologic, or dental treatment, with a poor outcome in all cases.

CONCLUSIONS: BDD is present and diagnosable in children and adolescents, and can cause significant morbidity. These preliminary data suggest that SRIs may be an effective treatment in this age group, although controlled treatment trials are needed to confirm this finding.

This work was supported in part by an unrestricted educational grant from Solvay Pharmaceuticals.

Poster No. 186

Clozapine Vs. Olanzapine Treatment of Childhood Onset Schizophrenia

Marianne Wudarsky, M.D., Ph.D.[1], Rob Nicolson, M.D.[2], Marge Lenane, M.S.W.[3], Jeffrey Bedwell, B.S.[4], Susan Hamburger, M.A., M.S.,[5] and Judith L. Rapoport, M.D.[6]

[1]Child Psychiatry Branch, NIMH, 10 Center Drive, MSC 1251, Building 10, Rm. 3N202, Bethesda, MD 20892; [2 3,4,5,6] Child Psychiatry Branch, NIMH, Bethesda, MD;

Olanzapine, a thienobenzodiazepine similar to clozapine with low D2 binding affinity is being used regularly for pediatric neuropsychiatric patients. Since 1990, NIMH has been studying typical and atypical agents for very early onset schizophrenia. A previous study compared treatment responses of Childhood Onset Schizophrenics (COS) receiving clozapine in open 6 week trials (N=15) with those receiving open 8 week trials of olanzapine (N=8). A higher response rate to clozapine was found at six weeks (p=0.01) (Kumra et al., 1998).

The present report is a comparison of 13 additional COS subjects' after 6 week open treatment with clozapine or 8 week open treatment with olanzapine.

METHODS: Children and adolescents with an onset of DSM-III-R schizophrenia by age 12 and who were treatment resistant to typical neuroleptics were admitted for open 6 week trials of clozapine (N=7) and open 8 week trials of olanzapine (N=6). The six week treatment response data was compared using baseline BPRS, SANS and SAPS scores as covariates.

RESULTS: At six weeks, clozapine treatment response was significantly greater (ANCOVA F=8.06; p=0.018).

DISCUSSION: As previously found, when comparing COS subjects' treatment responses in 6 week open clozapine trials to 6 week open olanzapine, clozapine appears more effective for this severely ill treatment refractory group. Limitations of this data analysis include comparing data from two separate treatment trials, differing trial lengths and small numbers of subjects. The on-going 8 week double-blind clozapine vs. olanzapine comparison of our severely ill, early onset cases may provide more valid data concerning the relative efficacy of these two agents.

Poster No. 187

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Poster No. 188

Deaths With Selective Serotonin Reuptake Inhibitor Treatment

Benjamin Roy, M.D., Sumner Goodman, M.D., Joseph Sacco, M.D., Reginald Peniston, M.D.

Stratton Albany VA Medical Center, 113 Holland Avenue, Albany, New York 12208

Because of their low potential for arrhythmias selective serotonin reuptake inhibitors (SSRIs) are deemed safe. However, no study controlled for the confounding effect of high protein binding of antidepressants to serum low density lipoproteins (LDL). Reduced LDLs increase while elevated LDLs obliterate free antidepressant. We collected mortality data retrospectively on 1000 unique patients examined between 1996 and 1998. Time of exposure to SSRI, dates of initiation of SSRIs, dates SSRIs were discontinued, and drug doses as well as, dates and values for serum cholesterol (91.7%) or LDL (33.9%) were determined by chart review and correlation with computer records. Patients were compared across different SSRIs with regard to serum cholesterol by a standardized ratio: [individual SSRI dose/ mean SSRI dose]/[individual serum cholesterol/mean serum cholesterol]. The mean ratio was calculated and three groups constituted: SSRI-naive patients, SSRI-treated patients <= 2SD, and SSRI-treated patients > 2SD. Deaths among SSRI-treated patients > 2SD [4/17 (23.5%)] was significantly higher than either SSRI-naive patients [14/531 (2.64%)] or SSRI-treated patients <= 2SD [7/378 (1.85%)]. Kaplan-Meier analysis of a computer randomized sample of 750 subjects was significant (Log rank = 18.00, df= 2, p< .0001). Cox regression analyses and Odds Ratio = 9.10, 95% Confidence Interval = 3.16-26.18 . Time of exposure to SSRIs was a mean 738 days, OR = 1.0, 95%CI = .9999-1.008. Two SSRI-treated patients > 2SD were on high dose SSRIs and had cholesterol > 290 mg/dl; while the remaining 2 patients were on ordinary doses with cholesterol < 100 mg/dl. Two patients complained of chest pain before their death while 2 died suddenly.

SSRIs and serotonin (5-HT) inhibit endothelial production of nitric oxide. Loss of endothelial-dependent vasodilation precipitates vasoconstriction to 5-HT and reduces coronary blood flow. SSRI-treated patients with LDL <= 110 mg/dl had a significantly higher incidence of chest pain than SSRI-naive patients (12/54 vs. 4/51; OR = 6.31; 95%CI = 1.58-25.21) with age as a cofactor (OR = 1.08; 95%CI = 1.02-1.15), and a paradoxically higher risk for chest pain than 10/110 SSRI-treated patients with hyperlipoproteinemia (OR = 3.27; 95%CI = 1.26-8.44).

Observational data has inherent biases. However, increased free SSRI due to reduced protein-binding to LDL or high doses that exceed protein-binding capacity may cause 5HT-induced microvascular spasm producing a syndrome of chest pain that is indistinguishable from angina pectoris due to coronary artery disease. The potential association with death requires confirmation by independent prospective investigation.

Poster No. 189

Hypertriglyceridemia and Endocrine Complications Associated with Propranolol Use in Psychiatric Patients

Jodi A. Worrel, Pharm.D.[1], Steven C. Stoner, Pharm.D.[1], BCPP, Rintu Khan, M.D. [2], Leonard Ramlatchman, B.S.Pharm., BCPP[2]

[1]UMKC School of Pharmacy, M3-C19 Medical School Building, 2411 Holmes Street, Kansas City, Missouri 64108
[2]Northwest Missouri Psychiatric Rehabilitation Center, 3505 Frederick Avenue, St. Joseph, Missouri

Background: The nonselective beta-blocker, propranolol, is used extensively in psychiatric patients for numerous off-label indications including tremor, akathisia, anxiety, and aggressive behavior. Propranolol has been associated with triglyceride (TG) elevations as well as blood glucose changes. Propranolol has not been associated with elevations in total cholesterol. Lipid profile changes associated with propranolol have not been systematically studied in psychiatric patients. The rationale of the following project is to examine lipid profile changes and possible endocrine complications associated with propranolol use in psychiatric patients.

Methods: A retrospective cohort analysis was performed. All inpatients treated with propranolol for a minimum of 6 months from January 1, 1993 to August 30, 1997 were identified. Available triglyceride and total cholesterol levels were averaged at baseline, 3, 6, 9, 12, 18, and 24 months after propranolol initiation or until a lipid lowering agent was initiated. The percentage change in available TG and total cholesterol levels from baseline was calculated for each patient at each time period. Changes in weight, concomitant medications, and initiation of adjunctive measures including dietary restrictions, lipid lowering agents, or antidiabetic agents were also recorded.

Results: A total of 11 patients were included in the study. All patients were male and the majority were Caucasian (n=8). The average age at propranolol initiation was 34 (SD=8.9). The median length of stay prior to propranolol initiation was 9 months. The majority of patients were receiving propranolol for the management of aggressive behavior (n=8). The average maximum propranolol daily dose was 216 mg (SD=134). The average individual percentage change in triglycerides was significantly greater than baseline at 6, 9, 12, and 24 months ($p < 0.05$). The average percentage change in TG levels initially peaked at 52% (SD=54) after 9 months (n=8). TG elevations persisted and at 24 months the average percentage change in TG levels was 109% (SD=126) over baseline (n=8). After propranolol initiation, six patients experienced average TG levels > 300 mg/dL versus two patients at baseline. Seven patients (64%) experienced at least a 40% increase in TG levels and 3 patients (27%) experienced dramatic TG elevations of over 100% from baseline. Adjunctive measures as described above were necessary for 8/11 patients. Two patients developed diabetes and another patient previously controlled on diet alone required antidiabetic medication after propranolol initiation. Of note, the patient who experienced the greatest change from baseline in TG levels (298% and 338% at 12 and 24 months, respectively) also developed diabetes and TG >1600 mg/dL after propranolol was increased from 360 to 480 mg/day 3.5 years after initiation. Propranolol was discontinued and both glucose and TG levels returned to normal allowing for discontinuation of lipid lowering and antidiabetic medications.

The percentage change in total cholesterol levels from baseline was not significant at any point over 24 months. Weight change was not significant at any point during the study except at 18 months after propranolol initiation (average weight gain=16$\pm$19 pounds, $p<0.05$).

Conclusion: The use of propranolol (216±134 mg/day) in psychiatric patients was associated with significant elevations in triglyceride levels and endocrine complications over long-term treatment.

Poster No. 190

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Poster No. 192

A Placebo-Controlled Study of Sertraline in Generalized Social Phobia

Michael Van Ameringen, M.D., McMasters University Medical Center, Hamilton, Ontario: Richard Swinson, M.D., McMasters University Medical Center, Hamilton, Ontario; John R. Walker, PhD, St.Boniface General Hospital, Wnnipeg, Maitoba; Roger M. Lane, M.D. Pfizer Inc., New York.

Objective: To evaluate the efficacy, safety, and tolerability of sertraline, a selective serotonin reuptake inhibitor, in the treatment of generalized social phobia.

Method: Following a 1-week, single-blind, placebo run-in, 206 adult outpatients with generalized social phobia from 10 Canadian centers were randomized to 20 weeks of double-blind treatment with sertraline or placebo in a 2:1 ration. The initial daily dosage of sertraline was 50mg with increases of 50mg/day every 3 weeks permitted after the fourth week of treatment (flexible dosing to a maximum of 200mg/day). Primary efficacy assessments were the percentage of patients much or very much improved on the Clinical Global Impression of Improvement (CGI-I) scale, and the mean total score baseline to endpoint change on the social phobia subscale of the Marks Fear Questionnaire and the Duke Brief Social Phobia Scale (BSPS).

Preliminary Results: 71 (53%) of 134 persons receiving sertraline and 20 (29%) of 69 persons receiving placebo were CGI-I responders at the end of treatment ($p<0.001$). Mean Marks Fear Questionnaire social phobia subscale and BSPS total score were reduced by 32.5% and 34.8% in the sertraline group and 8.6% and 16/7 in the placebo group ($p<0.005$), respectively. Sertaline-treated patents also evidenced significant improvements relative to patients receiving placebo on all secondary efficacy parameters and on social/leisure functioning and mental health dimensions of quality of life assessments ($p<0.05$). Overall, sertaline was well tolerated.

Conclusions: This study demonstrated sertraline to be an effective treatment for generalized social phobia. Future research should assess whether improvements may be maintained or further improved by either continued treatment or by augmentation with specific cognitive-behavioral techniques.

Poster No. 193

Risperidone and Suppression of Choreoathetosis in Huntington's Disease and Levodopa-Induced Dyskinesia in Parkinson's Disease

Mahmoud A. Parsa, M.D., [1] Heather M. Greenaway, R.N., [1] and Tandra S. Mangat, M.D., [1]

[1]University Hospitals, Department of Psychiatry,11100 Euclid Avenue, Cleveland, Ohio 44106

Introduction: Choreoathetois is a combination of jerky and slower sinuous involuntary movements associated with hyperdopaminergic states. Choreoathetosis is a major feature of Huntington's disease (HD), and is caused by the degeneration of nondopaminergic pathways that lead to a relative hyperdopaminergic state. Choreoathetosis can alo occur in patients with Parkinson's disease (PD) as a result of hyperdopaminergic state secondary to excessive levodopa therapy. In either cases, selective blockage of dopamine receptors may ameliorate the choreoathetoid movements. Risperidone is a novel atipsychotic agent with a balanced serotonin 5-HT2 and dopamine D2 receptor antagonism. Isolated case reports have suggested efficacy of risperidone in the management of tardive dyskinesia.

Objective: This study was intended to evaluate the suppressibility of choreoathtoid movements in HD and levodopa-induced choreoathetosis in PD, with risperidone therapy.

Method: Two groups of patients with choreoathetosis were treated with open-label risperidone. Riperidone was started at 0.5 mg/day, and increased as clinically indicated/tolerated by daily increments of 0.5 mg. The first group included 5 genetically confirmed HD patients, with moderate to severe motor abnormalities. Risperidone therapy was sustained for a period of 5 to 6 months. The Abnormal Involuntary Movement Scale (AIMS) and the Marsden and Quinn Severity Chorea Scale (MQSCS) measured changes in the severity of motor disability. The second group involved 3 patients with idiopathic PD, who suffered from levodopa-induced dyskinesia. Risperidone therapy was sustained for 3 to 4 weeks. The AIMS and the Simpson Scale measured changes in the severity of choreoathetosis and parkinsonism, respectively. In both groups, cognitive status was measured by the Mini-Mental State Examination (MMSE) at baseline and endpoint.

Results: All the HD patients showed dramatic improvment in choreoathetoid movements, with an average improvement of 65.1% on AIMS and an average improvement of 56.2% on MQSCS. Average dose of risperidone was 4.5 mg/day. All the PD patients showed a marked reduction in dyskinetic movements (as measured by a reduction from baseline to endpoint on the AIMS total score), without any significant worsening in parkinsonism. The risperidone dose ranged from 1 to 2 mg/day. There was no significant changs in the MMSE total scores from baseline to endpoint, in either HD or PD patients.

Conclusion: Our data suggest that risperidone was effective in the suppression of choreoathetid movemens in HD patients and levodopa-induced choreoathetosis in PD patients. Although PD patients required a lower dose range than HD patients, risperidone was well tolerated by both group of paients.

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Poster No. 194

A 12 Week, Open Trial of Donepezil Hydrochloride in Multiple Sclerosis Patients with Associated Cognitive Impairment

Yvonne M. Greene, M.D.,[1] Pierre N. Tariot, M.D.,[2] Heather Wishart, Ph.D.,[2] Christopher Cox, Ph.D.,[3] Connie J. Holt, B.S.,[2] Steven Schwid, M.D.,[4]

[1] Emory University Department of Psychiatry at Wesley Woods Geriatric Health Center, Fourth Floor, 1841 Clifton Rd NE, Atlanta, GA 30329-5102
[2] Department of Psychiatry, University of Rochester Medical Center, Rochester, New York
[3] Department of Biostatistics, University of Rochester Medical Center, Rochester, New York
[4] Department of Neurology, University of Rochester Medical Center, Rochester, New York

Background: Cognitive dysfunction occurs in up to 65% of patients with multiple sclerosis (MS), but there is no effective treatment for the symptoms. Cognitive impairment is a significant determinant of the quality of life for patients with MS, who have higher rates of unemployment, greater social isolation, and require greater personal assistance at home compared to cognitively intact MS patients.

Methods: We conducted a 12-week open pilot study assessing the efficacy and tolerability of donepezil HCl in MS patients with cognitive impairment. Seventeen patients (14 females, 3 males, mean age 55) at a long-term care facility with a Mini-Mental State Examination score (MMSE) of $\leq$ 25 received 4 weeks of 5 mg donepezil HCl followed by 8 weeks of 10 mg donepezil HCl. Cognitive, neurological, functional and behavioral assessments were conducted at baseline, 4 and 12 weeks.

Results: Total MMSE scores were significantly improved at week 0-4, week 4-12 and week 0-12 with an average increase at week 12 of 5.7 points. Change in performance on the recognition memory portion of the Hopkins Verbal Learning Test (true positives) was statistically significant when comparing week 0-4 and week 0-12. There was no significant difference in the sum of the three recall trials or the delayed recall trials, however. The subjects' severity of illness rating on the Clinical Global Impression of Change (CGIC) improved at both assessment periods with significance when comparing week 4-12 and week 0-12. Likewise, the impression of change rating on the CGIC statistically improved when comparing week 0-4 and week 4-12. Significant differences in performance were demonstrated on several additional tasks: Digit Span (forward + backward) at week 4-12 and week 0-12; Boston Naming Test sum of spontaneous and stimulus cue responses at week 0-4, week 4-12, and week 0-12; category portion of the Controlled Oral Word Association Test at week 0-12; recognition portion of the Motor Free Visual Perception Test at week 0-12; and the conceptualization subtest of the Mattis Dementia Rating Scale at week 0-12. No significant interactions were detected for neurological status or functioning as evidenced by scores on the Kurtzke Extended Disability Status Scale, Instrumental Activities of Daily Living, and Physical Self-Maintenance Scale. Subjects' behaviors improved at each of the assessment periods based on total Neuropsychiatric Inventory (NPI) scores. 81.3% of subjects who were symptomatic at baseline had a decrease in the NPI total score at week 12.

Significance: The results from this study suggest that donepezil HCl administration may be associated with significant clinical improvement in patients with MS who suffer moderate to severe cognitive impairment. The improvement was observed on average in performance on tasks assessing attention, memory, and conceptualization, with indications of improving efficiency on aspects of executive function. The clinical significance of these scale changes is supported by the global impression of change. Our data suggest that donepezil HCl merits further study as a potentially viable treatment option for the cognitive impairment associated with MS.

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